“A COMPARATIVE STUDY OF ORAL CLONIDINE AND ORAL MIDAZOLAM AS PREMEDICATION IN PEDIATRIC (4-12 YEARS) GROUP UNDERGOING TONSILLECTOMY”

A DISSERTATION SUBMITTED TO THE TAMILNADU
Dr. MGR MEDICAL UNIVERSITY

CHENNAI

In partial fulfilment of the Regulations

for the award of the Degree of

DOCTOR OF MEDICINE –BRANCH X ANAESTHESIOLOGY

DEPARTMENT OF ANAESTHESIOLOGY
TIRUNELVELI MEDICAL COLLEGE
TIRUNELVELI
MAY 2018

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Dr.J.BRIDGET MERLIN.M.D.,D.A.,D.N.B.,
Assistant Professor,
Department of Anaesthesiology,
Tirunelveli Medical College,
Tirunelveli

Date:
Place: Tirunelveli

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Date:
Place:Tirunelveli

Prof.Dr.R.AMUTHA RANI.M.D.,
Professor and HOD of Anaesthesiology,
Department of Anaesthesiology,
Tirunelveli Medical College,
Tirunelveli

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DEAN
Tirunelveli Medical College,
Tirunelveli

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Date:
Place: Tirunelveli

Dr.ASWATHY.B.S., MBBS.,
Postgraduate in Anaesthesiology,
Department of Anaesthesiology,
Tirunelveli Medical College,
Tirunelveli

ACKNOWLEDGEMENT

I am obliged to record my immense gratitude to **Dr.SithyAthiyaMunavarah.M.D.,** Dean, Tirunelveli Medical College Hospital for providing all the facilities to conduct the study.

I express my deep sense of gratitude and indebtedness to my respected professor Dr R. Amutha Rani MD Professor and HOD of Anaesthesiology ,Tirunelveli Medical College, Tirunelveli, whose valuable guidance and constant help have gone a long way in the preparation of this dissertation.

I am also thankful to my Professors **Dr.R.Selvarajan MD, Dr.E.Ebenezer Joel Kumar MD, DNB., Dr.G.Vijay Anand,M.D.,** for their help and valuable guidance.

I offer my special thanks to my guide Dr Bridget Merlin MD DA Assistant Professor & Head of Department, Department of cardiology for kind co-operation and valuable guidance.

I also offer my thanks to Dr Suresh Kumar MS ENT for helping me to conduct the study in tonsillectomy patients.

I express my thanks to all Professors, Associate Professors, Assistant Professors, Staff members of the Department of Anaesthesiology and all my Postgraduates colleagues, C.R.R.I s and friends for their help during my study and preparation of this dissertation and also for their co-operation.

I wish to acknowledge my parents and family members for their everlasting blessings and encouragement.

I thank all my patients who participated in this study for their extreme patience and kind co-operation.

Above all I thank the Lord Almighty for his kindness and benevolence.

Date:
Place: Tirunelveli

DrAswathy B.S.MBBS.,
Postgraduate in Anaesthesiology,
Department of Anaesthesiology,
Tirunelveli Medical College,
Tirunelveli

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TIRUNELVELI MEDICAL COLLEGE

INSTITUTIONAL RESEARCH ETHICS COMMITTEE
TIRUNELVELI, STATE OF TAMILNADU, SOUTH INDIA PIN 627011
91-462-2577733-EXT: 91-462-2572944; 91-462-2579785; 91-462-2572611-16
online@tvmc.ac.in, tirec@tvmc.ac.in; www.tvmc.ac.in

CERTIFICATE OF REGISTRATION & APPROVAL OF THE TIREC REF NO:919/ANS/2016

PROTOCOL TITLE : A COMPARATIVE STUDY OF ORAL CLONIDINE AND ORAL MIDAZOLAM AS PREMEDICATION IN PEDIATRIC (4-12 YEARS) GROUP UNDERGOING TONSILLECTOMY

PRINCIPAL INVESTIGATOR: Dr. B.S. ASWATHY, MBBS

DESIGNATION OF PRINCIPAL INVESTIGATOR: POST GRADUATE IN ANAESTHESIOLOGY

DEPARTMENT & INSTITUTION: TIRUNELVELI MEDICAL COLLEGE, TIRUNELVELI

Dear , Dr. B.S.Aswathy, The Tirunelveli Medical College Institutional Ethics Committee (TIREC) reviewed and discussed your application during the IEC meeting held on 05.08.2016.

THE FOLLOWING DOCUMENTS WERE REVIEWED AND APPROVED

1. TIREC Application Form ☐
2. Study Protocol ☐
3. Department Research Committee Approval ☐
4. Patient Information Document and Consent Form in English and Vernacular Language ☐
5. Investigator's Brochure ☐
6. Proposed Methods for Patient Accrual Proposed ☐
7. Curriculum Vitae of the Principal Investigator ☐
8. Insurance /Compensation Policy ☐
9. Investigator's Agreement with Sponsor ☐
10. Investigator's Undertaking ☐
11. DCGI/DGFT approval ☐
12. Clinical Trial Agreement (CTA) ☐
13. Memorandum of Understanding (MOU)/Material Transfer Agreement (MTA) ☐
14. Clinical Trials Registry India (CTRI) Registration ☐

THE PROTOCOL IS APPROVED IN ITS PRESENTED FORM ON THE FOLLOWING CONDITIONS

1. The approval is valid for a period of 2 year/s or duration of project whichever is later
2. The date of commencement of study should be informed
3. A written request should be submitted 3weeks before for renewal / extension of the validity
4. An annual status report should be submitted.
5. The TIREC will monitor the study
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   b. The PI must comment how proposed amendment will affect the ongoing trial. Alteration in the budgetary status, staff requirement should be clearly indicated and the revised budget form should be submitted.
   c. If the amendments require a change in the consent form, the copy of revised Consent Form should be submitted to Ethics Committee for approval. If the amendment demands a re-look at the toxicity or side effects to patients, the same should be documented.
   d. If there are any amendments in the trial design, these must be incorporated in the protocol, and other study documents. These revised documents should be submitted for approval of the IEC, only then can they be implemented.
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   f. The amendment is unlikely to be approved by the IEC unless all the above information is provided.
   g. Any deviation /violation /waiver in the protocol must be informed.

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Registrar, TIREC
Tirunelveli Medical College, Tirunelveli - 627011
State of Tamilnadu, South India

Dr.J.Suresh Durai, MD
Member Secretary, TIREC
Tirunelveli Medical College, Tirunelveli - 627011
State of Tamilnadu, South India

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This is certify that this dissertation work title **"A COMPARATIVE STUDY OF ORAL CLONIDINE AND ORAL MIDAZOLAM AS PREMEDICATION IN PEDIATRIC (4-12 YEARS) GROUP UNDERGOING TONSILLECTOMY"** of the candidate **Dr.ASWATHY.B.S.,** with registration Number **201520302** for the award of M.D.in the branch of **ANAESTHESIOLOGY.** I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion page and result shows **8 percentage** of plagiarism in the dissertation.

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INTRODUCTION

A need exist for an efficient premedicant drug especially in paediatric age group undergoing elective surgical procedures. Anxiety and fear of operation, injections, physicians, operation theater environment, and parental separation are all traumatizing experiences in young children resulting in postoperative maladaptive behavioral changes .Premedication[1] should yield a patient who is calm, free of anxiety and pain, sedated, but easily arousable and fully co-operative. The concept of premedication was introduced in early 1900s.The administration of drugs before the induction and maintenance of anaesthesia is reffered to as Preanaesthetic medication .The term premedication was first used in the 1920s..One of the ,commonly used premedicant in paediatric anaesthesia drug worldwide is midazolam[2]. Clonidine ,an alpha 2 agonist ,central sympatholytic agent used as antihypertensive agent is a new trial in this category[3.4]. Inspite of all existing premedicants anaesthetic practitioners are still in search for an ideal premedication agent with better efficacy and minimal side effects .So I decided to compare the efficacy of midazolam and clonidine as oral premedication in children undergoing elective tonsillectomy.

AIM OF THE STUDY

To compare the clinical effects of oral midazolam and oral clonidine as premedication in children undergoing tonsillectomy .The preoperative sedation, anxiolysis, acceptance of mask for induction of anaesthesia, intravenous cannulation and post operative recovery were assessed in both groups.

PREMEDICATION

The major objective of premedication is to decrease the stress response without affecting the hemodynamic stability [1,2,3].

The aims of premedication are

1. To relieve fear and anxiety

2. To promote amnesia and sedation

3. To facilitate rapid and smooth induction of anesthesia

4. To decrease the secretions of the respiratory tract

5. To reduce the risk of aspiration pneumonitis by reducing the volume of gastric contents and increasing the pH.

6. To minimize the bradycadia and sympathetic activity which results from surgical stimulus or anaesthetic techniques.

7. To reduce the sympathetic system reflex activities

8. To minimize the requirements of anaesthetic agents

Properties of an ideal premedicant agent

1.Easily administered

2.Safe to the patient

3.Should not prolong the postoperative recovery period

4.,Should preserve heamodynamic stability ,

5.Should not depress the cardiovascular system and central nervous system

Various routes of administration of premedication [1]

1) Oral administration
   Eg. clonidine, midazolam, triclofos, ketamine

2) Intramuscular administration
   Eg. opioids, benzodiazepines, anticholinergics, H2 blockers

3) Intravenous administration
   Eg. opioids, benzodiazepines, anticholinergics, antiemetics

4) Intra nasal administration
   Eg. midazolam, ketamine, sufentanil

5) Rectal
   Eg. Methohexital, thiopentone sodium

6) Oral transmucosal administration
   Eg. Midazolam, oral transmucosal fentanyl citrate

Route of administration varies according to time and action required Intravenous injections are given seconds before induction where as oral drugs or intramuscular , subcutaneous injections given 30-45min preoperatively or at an appropriate time.

Factor affecting choice of premedication

1.Patients age, body weight, physical condition and psychological status.

2.Nature ,site and duration of proposed surgery

3.Availability of preoperative and post operative care unit.

4. Surgical and anaesthetic management available.

The common routes of administration of premedication are intravenous, intramuscular and oral.

Oral premedication :

Advantages :

1.Commonly used route

2. Easy to administer

3. Economical

4. safe

Disadvantage :

1. Delayed onset of action of drug
2. Absorption get affected in presence of food or other drugs and due to physical characteristics of the drugs(decreased bio availability).
3. Gastro intestinal mucosa irritation may result in emesis.
4. Difficult to administer in unconscious and uncooperative patient.

Premedication should be administered with special care in certain disease states. Patients with adreno cortical, thyroid and pituitary insufficiency, hepatic or renal dysfunction and myasthenia gravis has increased sensitivity to certain drugs. Acute exacerbation of porphyria resulting in abdominal pain, vomiting, haematuria, paralysis and even respiratory failure is caused by use of barbiturates.

Premedication in children :

The preoperative period is a stressful period both in case of adults and children.But unlike adults who needs better anxiolysis and anterograde amnesia in children we as anaesthethist are more concerned about separation anxiety, fear for needle pricks, change in bodily Image and delayed post operative recovery .The main goal of the premedication in pediatric surgery is the safe induction of anaesthesia with minimum stress and risk to the child.

Special concerns in paediatrics

1. Increase in vagal activity

2. Vomiting and aspiration

3. Secretion

4. Respiratory depression

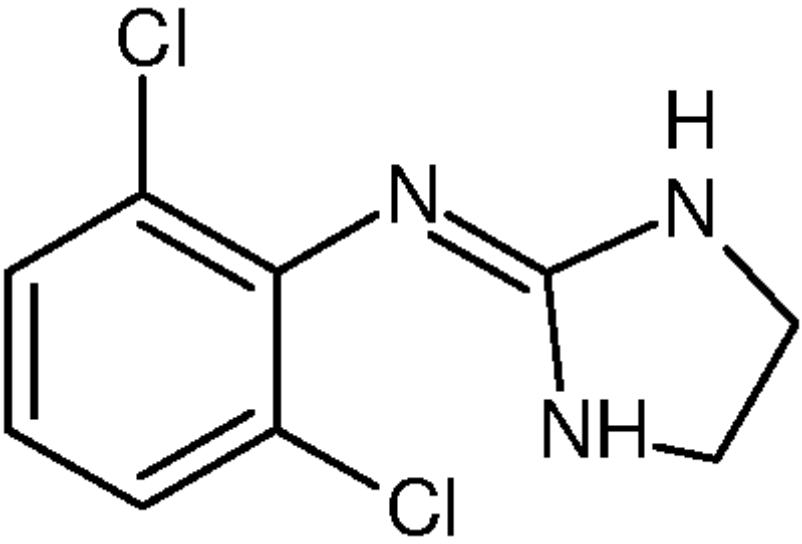
PHARMACOLOGY OF CLONIDINE [3,4]

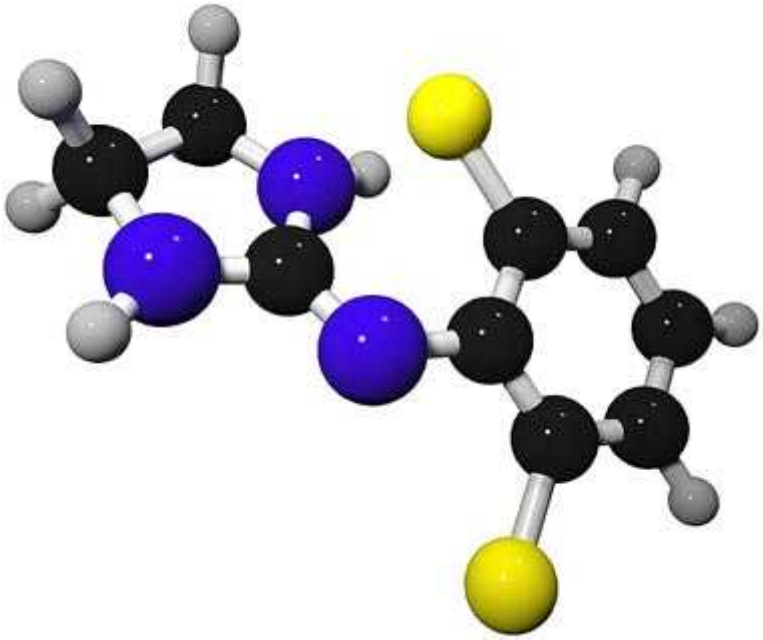
Clonidine is a central sympatholytic agent. It is an alpha-2 agonist commonly used as a antihypertensive agent. As it has sedative , hypnotic and analgesic properties it is been used in anaesthesiology.

Structure Activity Relationship[3,4]

It is an imidazoline derivative and related to adrenergic alpha agonist naphazoline and antagonist tolazoline and H1 antagonist antazoline.It has the properties of all these three .It is a selective agonist for alpha2 receptor with a ratio of 200 : 1 (alpha2 : alpha 1) and it is a partial agonist. It has a molecular weight of 266.56 .Clonidine hydrochloride is an odourless, bitter, white, crystalline substance soluble in water and alcohol .It was introduced in the early 1960's as a nasal decongestant. The antihypertensive property of the drug was found during this period.

Molecular structure of Clonidine[Fig:1]





PHARMACOKINETICS

The bioavailability of clonidine is nearly 100%.Therefore it is rapidly and completely absorbed after oral administration .The Peak plasma concentration is reached with in 60-90 minutes after administration and maximal effects are observed 1-3 hours after an oral dose. The elimination half life is around 6-24 hours (mean 12 hours) . About 50% of the drug is metabolized in the liver into active metabolites where the rest is excreted unchanged by the kidney.

MECHANISM AND SITE OF ACTION [3,4,5]

Sedation was a side effect of clonidine when used as Antihypertensive agents. This disadvantage became an advantage anesthetic point of a premedication agent The locus ceruleus situated in the upper brainstem in the floor of the fourth ventricle is the major site of action for this sedative / hypnotic drug .The activation of Alpha 2 recceptors causes inhibition of adenylcyclase which in turn will prevents the conversion of ATP to AMP .thus it decreases the calcium entry into the neuron terminals and inhibits exocytosis of stored neurotransmitters from the synaptic vesicles .The stimulation of postsynaptic alpha 2 receptors in CNS produces sedation and decreased sympathetic outflow which leads to peripheral vasodilatation and lowers the BP. It has got half life of 12 to 24 hrs . It has majority of its afferent connection from the rostral ventro lateral medullary nuclei. It has three important sets of efferent.

1.Noradrenergic fibres connecting the sub thalamic nuclei and the thalamus with consequent effects on cortical activity.

2.Fibres to the descending reticular formation with connections to the pressor and depressor areas of vasomotor centres.

3.Descending fibers to the reticulospinal tracts which inhibits pain transmission at the level of spinal cord

Alpha-2 agonist hyperpolarize the neurons of locus ceruleus through the potassium channels.

PHARMACO DYNAMICS[3,4.5]

Central nervous system :

Clonidine produces sedation and anxiolysis by acting on locus ceruleus. Its sedative effect is potentiated by benzodiazepines .Anxiolysis produced is comparable to that produced by benzodiazepine. It may produce anxiogenic responses through nonselective activation of alpha -2 receptor at higher doses .It produces a potent analgesic response involving both supra spinal and spinal sites .It reduces the minimum alveolar concentration of halothane by 20-50% in dose dependent fashion there by reducing anaesthetic requirements .When used as an adjuvant in peripheral nerve blocks and subarachnoid block it will prolong the duration of block .Clonidine reduces the intra ocular pressure by acting on imidazole preferring receptor (IPR) by reducing the production of aqueous humour .Cerebral protective effect against

cerebral ischemia results from action on imidazole preferring receptor (IPR) than alpha-2 receptor.It also decreases the cerebral blood flow. It reduces the post operative shivering .it helps in attenuating opioid withdrawal symptoms at a dose of 0.3 mg / kg 2 to 4 times a day. It is said to decrease the fentanyl induced muscle rigidity .It is a choice of drug in chronic pain syndrome .It is used in alcohol withdrawal symptoms and smoking cessation. Clonidine decreases vasomotor symptoms of menopausal syndrome. Clonidine has been used to control diarrohea due to diabetic neuropathy. Clonidine suppression test for pheochromocytoma :Clonidine reduces plasma noradrenaline concentration to< 0.5 ng/ml in patients of essential hypertension but not in those with pheochromocytoma Clonidine can be used to control tics in tourette syndrome

DRUG INTERACTION :

When clonidine is given along with nonselective beta blockers ,blood pressure increases due to unopposed alpha action leading to vasoconstriction .Tricyclic antidepressants and chlorpromazine abolish the antihypertensive action of clonidine probably by blocking alpha receptors on which clonidine acts. Atropine is the drug of choice for clonidine induced bradycardia, but large doses of oral clonidine such as 5ug/kg attenuate the effect of atropine. The clonidine potentiate the pressor effect exerted by ephedrine .Rebound hypertension occurring when clonidine is stopped results from increase in nonadrenaline release which is inhibited by these agents owing to their agonist effect on presynaptic alpha receptor.

DOSAGES

Oral : 3-5mcg/kg

IV: 1-3 mcg/kg

IM: 2mcg/kg

Transdermal: 0.1-0.3 mg release per day.

Intrathecal ; 75-150 mcg

Epidural ; -2 mcg/Kg

PHARMACOLOGY OF MIDAZOLAM[2,3,5,6]

Midazolam was synthetised by Fryer and Walser in 1976. It was the first clinically used benzodiazepine that was water soluble. Midazolam is the only benzodiazapine used for prolonged administration when rapid recovery is required.

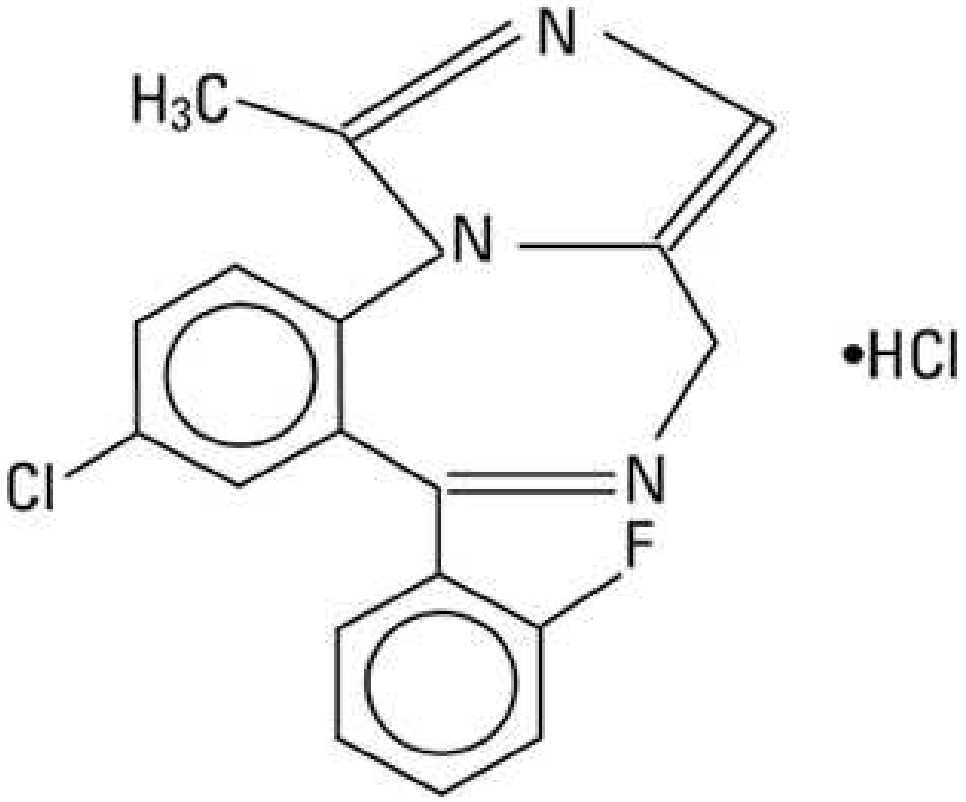
STRUCTURE :

Midazolam is a water soluble drug with imidazole ring which makes it stable in aqueous solutions ,water soluble and helps in rapid metabolism[2,3,6]. Benzyl alcohol is common preservative added. Preservative free midazolam is also available. PH of the parenteral form of midazolam is 3.5(Buffered). It has pH dependent solubility i.e. if pH is more than 4 it is lipid soluble and if pH is less than 4 it is water soluble. Molecular weight of midazolam is 362 and pKa : 6.15

METABOLISM :

Midazolam is metabolized to 1 and 4 hydroxymidazolam by oxidative pathway by cytochronic P 450 (cyp 3A450enzymes) in the liver[2]. 1 hydroxy midazolam is the principal metabolite and has half the activity of parent molecule But these are rapidly conjugated to glucuronic acid and excreted in urine .Therefore there want be prolonged action after single dose .This glucuronide has higher pharmacological activity at higher concentration.

Molecular structure of midazolam[Fig:2]



PHARMACOKINETICS :

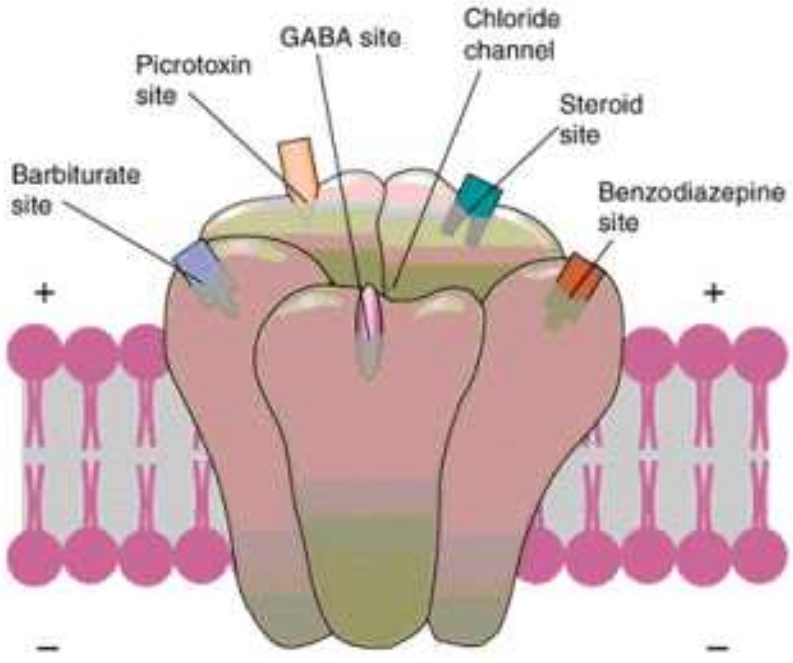
Midazolam is rapidly absorbed from the GIT. Only 50% of bioavailability due to first pass metabolism About 95% bound to albumin .Its volume of distribution is 1.1 - 1.7 L/kg. Elimination half life is 1.7 - 2.6 hour Clearance is 6.4 – 11 ml / kg / min Plasma level required for hypnosis and amnesia during surgery are 100 – 200 ng/ml [4] .Highly Lipid soluble and crosses blood brain barrier but redistribution to inactive tissue leads to its short duration of action .Awakening usually occurs at a level lower than 50 ng/ml .Older age , obesity and renal failure prolong the elimination half life.

MECHANISM OF ACTION :[6]

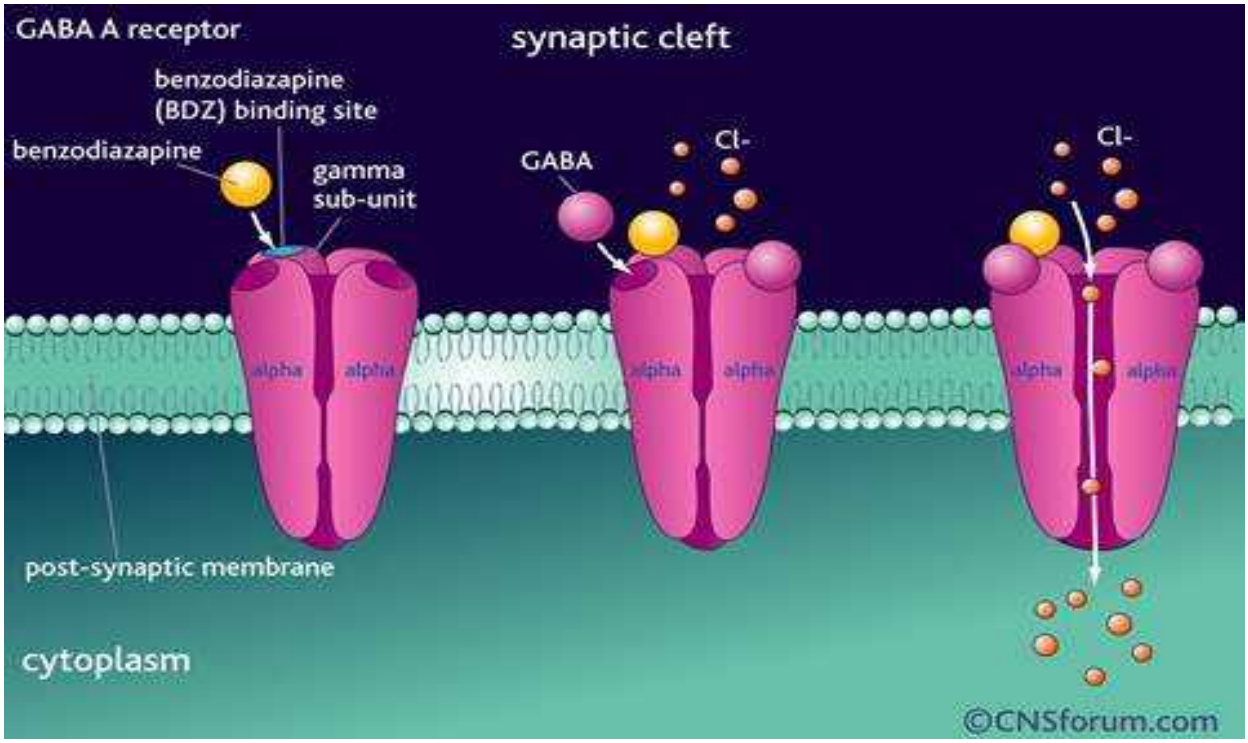
Midazolam, makes its action by facilitating interaction of GABA A with (GABA)A chloride ionophore [2,4] .It binds to BZD receptor γ subunit and increases the affinity of receptor of GABA resulting in increased frequency of opening of GABA . This will lead to increased chloride ion conductance which causes hyperpolarization and resistance of post synaptic membrane to neuronal transmission .Various effects of benzodiazepines is related to amount of receptor occupancy which corresponds to plasma concentration .Alpha 1 and 5 for sedation ,Alpha 2 and 5 for anxiolysis. If receptor occupancy is 20%, it causes anxiolysis. If receptor occupancy is 30-50%, it causes sedation If receptor occupancy is > 60%, it causes unconsciousness.

FIG [3]

► **Schematic Illustration of a $GABA_A$ Receptor, with Its Binding Sites**



Fig[4]


GABA A receptor
synaptic cleft
benzodiazapine
(BDZ) binding site
benzodiazapine
gamma
sub-unit
GABA
Cl-
Cl-
alpha
alpha
alpha
alpha
alpha
alpha
post-synaptic membrane
cytoplasm
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PHARMACOLOGICAL ACTION [3,5,6]

Onset is around 30 – 60 sec after giving IV 15 – 30 min after giving oral .Duration of action is 30 – 60 min when given IV 45 – 90 min when given as oral

Effect on Central nervous system :

Midazolam is found to produce sedation, anxiolysis, anticonvulsant effect, muscle relaxation and unconsciousness. These effects are dose dependent .It is based on percentage of receptor occupancy. It produces anterograde and not retrograde amnesia .A dose related reduction in cerebral blood flow and CMRO2 is also there . It has cerebral protective effect is superior to diazepam but inferior to barbiturate. Cerebral vasomotor response to CO2 is preserved. It does not prevent increases in intracranial pressure following tracheal intubation. It's a potent anticonvulsant.

Effect on respiratory system :

Midazolam produces ventilatory depression that is dose related and is greater than that of other benzodiazepines. It is more pronounced by fast intravenous administration along with any opioids .It is not seen when given through other routes like oral. The onset of respiratory depression is within 3 minutes and this action lasts longer for about 60-120 minutes on intravenous administration. The Slope of ventilatory response curve to carbon dioxide is found to be flatter than normal. Incidence of apnea is is greater in old age, debilitated state, COPD patients and in presence of intake of other respiratory depressants drugs.

Effect on cardiovascular system:

It decreases arterial pressure by decreasing systemic vascular resistance and not by affecting the cardiac output. In hypovolemic state it produces exaggerated fall Its effect on systolic BP depends on plasma concentration

Effect on Fetus

The placental transfer of midazolam is lesser than other benzodiazepines. It is found that midazolam produces greater neonatal depression than thiopentone and propofol.

Drug interactions :

Erythromycin inhibits the metabolism of midazolam and prolong and intensify its effects .Antifungal agents like itraconazole, ketaconazole increases the serum concentration of midazolam .Calcium channel blockers inhibit the cytochrome P 450 enzymes which in turn lead to central nervous system depression .Clonidine inhibits metabolism of midazolam .The sedative effects of midazolam is potentiated by ethanol, barbiturates .Alpha 2 agonists opioids and other central nervous system depressant drugs The minimum alveolar concentration of volatile agents are reduced by30%.Hepatic clearance is inhibited by fentanyl. Hepatic clearance is 5 times greater than lorazepam and 10times greater than diazepam.

Routes of Administration [1,6]

The most commonly used route is intravenous. Intramuscular route for sedation, oral route for premedication, intranasal and rectal routes for premedication in children.

DOSAGE:

Oral: 0.25 - 0.75 mg/kg

Rectum: 0.25 – 0.5 mg/kg

Intranasal: 0.2 – 0.5 mg / kg

Intramuscular: 0.1 – 0.2 mg/kg

Intravenous: 0.025 – 0.1 mg /kg

Sublingual: 0.1 -0.2mg / kg

SIDE EFFECTS :

Respiratory depression is the major side effect following intravenous route especially with fast administration of drug along with other opioids. Therefore respiration should be monitored after giving the drug.

CLINICAL USE [3,6]

Premedication:

Midazolam is the widely used premedicant in children, especially in oral formulation which was approved by the US food and drug administration in 1998.Oral dose of 0.25-0.5 mg/kg can be given 30 minutes before surgery for sedation and anxiolysis [2,6] It has got bitter taste which can be mask by adding sugar solution .2mg/ml syrup forms are available .Advantage is that there is minimum ventilator depression and SPO2 fall at 1mg/kg .Anterograde amnesia is present

Intravenous sedation :

Midazolam in dose of 1.5-2.5 mg can be used for procedures with onset of action in 30-60 seconds ,peak effect in 5 minutes and duration of action for 15 -80 minutes It is water soluble, minimal venous irritation, rapid onset, short duration and less postoperative sedation.

Induction and maintenance of anaesthesia :

It is the benzodiazepine of choice as an induction agent. Intravenous administration of midazolam in doses of 0.05-0.15 mg/kg over 60 seconds will produce induction of anaesthesia [4].It is faster when premedicated with opioids or any CNS depressants .It is used to supplement opioids or inhaled anaesthetics during maintenance of anaesthesia. It reduces the anesthetic requirement of halothane by 30%

Maintainance of Anaaesthesia

It is used along with opioids ,propofol and inhalational agents for maintenance in dose of 0.05mg/kg or1mcg/kg/hr.Patient wakening is prolonged 2.5 times than that of Thiopentone

Post Operative sedation

Midazolam can be used in the loading dose of 5 mg/kg iv bolus and then maintenance of 0.15 mg/kg /hr for post operative sedation in intubated patients

Paradoxical Vocal Cord Motion

It causes non organic upper airway obstruction and stridor post operatively. Inj Midazolam 1-2 mg IV can be helpful [6]

REVIEW OF LITERATURE

Almenrader N, passariello Mcoccetti b heiberger etal [9] Pediatric journal of Anaesthesiology " 2007 Dec;17(12):1143-9." Premedication in children: a comparison of oral midazolam and oral clonidine". They conducted a prospective open study in 64 children who were randomly assigned to receive either oral midazolam 0.5 mg.kg (-1) (group M) or oral clonidine 4 microg.kg (-1) (group C) prior to the mask induction .They evaluated the Drug acceptance, preoperative sedation and anxiolysis, quality of mask acceptance, recovery profile and parental satisfaction **.**The taste of oral clonidine was judged as significantly better; 14% of children rejected oral midazolam. Onset of sedation was significantly faster in those premedicated with midazolam than with clonidine. The level of sedation was significantly better after premedication with clonidine. Quality of mask induction was comparable in both groups .They observed a increasing trend in emergence agitation after premedication with midazolam .There conclusion was that premedication with oral clonidine appeared to be superior to oral midazolam. Oral clonidine was better accepted by the child, produced more effective preoperative sedation, had better recovery from anesthesia.

Lisa Fazi, MD, Ellen C. Jantzen, MD, John B. Rose, MD, C. Dean Kurth,MD, and Mehernoor F. Watcha, MD [10] Anesthesia analgesia 2001,92;56-61"A comparision of oral clonidine and oral midazolam as preanaesthetic medications in pediatric tonsillectomy" The study was to compare the effects of oral clonidine (4 ug/kg) and midazolam (0.5mg/kg) on the preanesthetic sedation and postoperative recovery profile in children during tonsillectomy. In a double-blinded, double-dummy study design, 134 ASA physical status I-II children aged 4-12 yr were recruited. They were divided into 2 groups to receive a combination of either clonidine and placebo (Group A), or placebo and midazolam (Group B) at 60-90 min and 30 min, respectively, before the induction of anesthesia Midazolam was superior to c1onidine as oral preanesthetic medication for these patients.

Frank T, Wehner M, Heinke W, Schmadicke I (Feb 2002)NCBI ;PUBMED .gov 2002 feb 37(2) 89-93[11] .A comparision of the anxiolytic effect of clonidine and midazolam as a premedication. The anxiolytic effect of clonidine with midazolam were compared 50 patients (ASA I, II, III) were included in the study. It was a double blinded, prospective study. They recieved oral premedication with 1 mg flunitrazepam in the evening before surgery and 5 ug/kg clonidine or 100ug/kg midazolam 60-90 minutes before surgery. They recorded the degree of anxiety before and after premedication. The clonidine showed a anxiolytic effect which is comparable to midazolam. Therefore they concluded that clonidine is good alternative to benzodiazepines as premedication.

Galletti, C.; Genovese, A.; De Salvo, G.; Trimarchi, G.; Mazzeo, G.; Mandolfino, T.[12].european journal of anaesthesiology June 2013,volume 30,pages 24-25 .The study was conducted in a group of 24 pts who received oral clonidine 3 mcg/kg 60-90 minutes before surgery and a group of 24 patients who received oral midazalom 0.5 mg/kg 60-90 minutes before surgery. The objective of the study was to evaluate the clinical effects like anxiolysis sedation and analgesia on administration of both oral premedicants. They concluded from their study that oral clonidine premedicated patients underwent adeno-tonsillectomy with better outcome than oral midazolam. Oral clonidine provided better sedation, better face mask acceptance, without any clinically significant PONV. They also had significantly reduced values of pain and postoperative agitation.

† N. Tazeroualti F. De Groote S. De Hert A. De Villé A. Dierick P. Van der Linden[13] British Journal of Anaesthesia, Volume 98, Issue 5, 1 May 2007, Pages 667–671, Oral clonidine *vs* midazolam in the prevention of sevoflurane - induced agitation in children. This is a prospective randomized, double-blinded control study done to test the hypothesis that, in comparison with midazolam, premedication with oral clonidine reduces the incidence of emergence agitation in preschool children anaesthetized with sevoflurane. Sixty-eight ASA I–II children planned for circumcision were randomized into three groups to receive different oral premedication given 30 min before anaesthesia: midazolam 0.5 mg kg^{-1}, clonidine 2 µg kg^{-1}, and clonidine 4 µg kg^{-1}.

Sevoflurane anaesthesia was administered via a facemask (O_2/N_2O: 40/60). Analgesia was with penile block (bupivacaine 0.5% 0.3 ml kg^{-1}) and rectal paracetamol (30 mg kg^{-1}). During the first postoperative hour, children were evaluated using a modified 'objective pain scale'.They concluded that in comparison with midazolam, clonidine 4 µg kg^{-1} reduced sevoflurane-induced emergence agitation without increasing postoperative side-effects

Andre p. Schmidt MD,Valinetti MD phd,denise Bandeira ,Maria F Bertacchi MD,Claudia mSimoes MD Jose otavio c.Auler JR MD [14] Volume 17, Issue 7 July 2007 Pages 667–67 **"**Effects of preanesthetic administration of midazolam, clonidine, or dexmedetomidine on postoperative pain and anxiety in children" The aim of this study was to evaluate the action of three different premedication regimens on postoperative pain and anxiety in children. A prospective, randomized, open-label clinical trial in 60 school children. They were randomized for premedication with oral midazolam 0.5 $mg \cdot kg^{-1}$, oral clonidine 4 $\mu g \cdot kg^{-1}$, or transmucosal dexmedetomidine 1 $\mu g \cdot kg^{-1.}$ The pre- and postoperative evaluation of anxiety was done with the State-Trait Anxiety Inventory for Children and asked to report any pain in verbal and visual analog scales. They concluded that children receiving clonidine or dexmeditomidine preoperatively have similar levels of anxiety and sedation postoperatively as those receiving midazolam. However, the group given α_2-agonists had less perioperative sympathetic stimulation and less postoperative pain than those given midazolam.

Sequeira Trevor, Madhusudan Upadya, Chandni Sinha,and Manpreet Kaur[15] Saudi Journal of Anaesthesiology 2012 Jan-March 6(1) 8-11" A comparison of midazolam and clonidine as oral premedication in pediatric patients" The aim of the study was to compare oral midazolam (0.5 mg/kg) versus oral clonidine (4 μg/kg) as a premedication in pediatric age group 2-12 years with regard to sedation and anxiolysis .The pediatric patients belonging to the American Society of Anesthesiologists class I and II between the age group of 2-12 years scheduled for elective surgery were randomly allocated to receive either oral midazolam (group I) 30 min before induction or oral clonidine (group II) 90 min before induction of anesthesia. They were evaluated for levels of sedation and anxiety at the time of separation from the parents, venopuncture, and at the time of mask application for induction of anesthesia .Their conclusion was that oral midazolam is superior to clonidine as an anxiolytic in pediatric population. Clonidine with its sedative action especially at the time of separation from parents along with its other perioperative benefits cannot be discount

Anupam Das Kishore Das Minoti Baruah Manigreeva Krishnatreya Amal Chandra Katak[16] International Journal of Research in Medical Sciences June 2016;4(6):2341-2347 **"**Oral premedication for pediatric Anaesthesia a comparison between midazolam and clonidine ."This was a prospective observational study was carried out in a tertiary care hospital 2005-2006) . The study was conducted in children undergoing surgery under general anaesthesia in age group 2-10 years. Sixty children were divided into two groups, in one group patients received oral midazolam and other group received oral clonidine as premedicant .They concluded that oral midazolam has better efficacy in terms of preoperative sedation and oral clonidine had stable hemodynamic profile and better analgesia in the clonidine group

Javaher Froosh F ,m Raa Pipelzadah et al [17] pak medi net ,Pakistan journal medical science October – Dec 2009 25(5) 782-5 *:"* Clonidine reduces post operative nausea and vomiting in laparoscopic gynecological surgeries".This was a prospective double blind study done to evaluate the efficacy of oral clonidine in preventing post operative nausea and vomiting patients undergoing laparoscopic gynecological surgeries. A group of 86 patients ASA class one or two were selected .They were equally divided into 2 groups The study group (n=43) received clonidine 0.2mg tablet with 50ml water 60–90 minutes before surgery while the control group(n=43) received placebo (the tablets were made at Ahwaz Pharmaceutics Department). Both the groups were monitored for 24 hour post-operatively for presence of PONV. Hemodynamic changes after intubation between these groups were compared.

Sedation and pain scores were also recorded during recovery using Ramsay score and by visual analogue scale respectively .They found that Clonidine had statistically significant effect in reducing incidence of both nausea and vomiting.It also has a positive outcome on post operative pain score.

Mikawa. K, Maekawa N, Nishina K, Takao Y, Yaku H, Obara H [18] NCBI; pubmed .gov.1993 nov ,79(5) 926-31 Efficacy of oral clonidine premedication in children It was a prospective, randomized, controlled clinical trial.It was double blinded study of 105 children, within the age group of 4-12 years posted for elective ophthalmological surgery .They received 2µg/k or 4 µ/kg of oral clonidine or 0.4mg/kg oral diazepam given 105 min prior to the induction of anaesthesia They also recieved 0.03 mg / kg oral atropine 60 min before anaesthesia. A blinded observer noted the children's level of sedation, quality of separation from parents, and degree of mask acceptance during inhalation of nitrous oxide used for establishing venous assess. All of them were induced with 5 mg/kg thiopentone and muscle relaxant used was 0.2 mg / kg vecuronium. They concluded that even in pediatric anaesthesia, the combination of 4 µg / kg oral clonidine and 0.03 mg/kg atropine is an effective premedication.

Katsuya Mikawa1 ,Kahoru Nishina1,Nobuhiro Maekawa1,Migiwa Asano1 and Hidefumi Obara[19] NCBI;pubmed.gov can journal of anesthesia 1995, nov ;42(17)977-81 “Oral clonidine premedication reduces vomiting children after strabismus”.The study was conducted to determine whether the preoperative orally administered clonidine causes or potentiates postoperative vomiting .It was a prospective randomized double-blind trial done in 140 children (3–12 yr) undergoing strabismus surgery. The conclusion of the study was that preanaesthetic medication with clonidine 4 μg kg−1 may be useful in preventing emesis following strabismus surgery. Clonidines this property shows that it may be superior to other sedative premedicants such as diazepam and midazolam.

Ramesh VJ, Bhardwaj N, Batra YK (May 1997) [20] NCBI; pubmed .gov international journal of anesthesiology 1997,may 75(5) 218-21” Comparitive study of oral clonidine and diazepam as premedicants in children”. It is a prospective, double blinded, controlled study in which the efficacy of clonidine and diazepam as oral premedication in children ,was compared .The comparision was done with respect to sedation, intubation response and recovery in 50 children, aged 4– 12 years, undergoing general anaesthesia. Clonidine 3ug/kg produces sedation comparable to diazepam 0.2 mg/kg .It also reduces the intubation response without increasing the incidence of complications.

Saikat Majumdar, Anjan Das, Haripada Das, Sambhunath Bandyopadhyay, Bimal Kumar Hajra,] Dipankar Mukherjee [21] Perspective in Clinical research 2015 Oct-Dec 6(4) pages211-216 " Comparative evaluation of oral gabapentin versus clonidine as premedication on preoperative sedation and laryngoscopic stress response attenuation for the patients undergoing general anesthesia". The aim of the study was to compare the BP, HR during laryngoscopy and intubation as well as to evaluate the preoperative sedation status between oral clonidine and oral gabapentine as premedication for patients undergoing major surgery under general anesthesia . It was a prospective, double-blinded, and randomized controlled study; conducted in 100 adult patients of either sex, aged 20-45, of ASA I and II undergoing major surgery of >1 hour duration .They were randomly allocated into groups C and G were pre treated with oral clonidine (200 µg) and gabapentin (800 mg) respectively 2 hours before induction. Preoperative sedation and haemodynamic parameters were monitored .They concluded that oral clonidine is comparable in producing preoperative sedation to oral gabapentin, at the same time oral clonidine is more efficacious in reducing laryngoscopic stress response than oral gabapentin.

Evaoddby Muhrbeck et al [22] NCBI ;Pubmed.gov anesthesiology 2002,may 96(5)1109-14 **"**Effects of clonidine on post operative nausea and vomiting in breast cancer surgery" Sixty-eight women were premedicated with midazolam were randomly allocated to coinduction with intravenous clonidine (group C) or placebo(group P). It is a prospective, double-blind study. Anesthesia was standardized (laryngeal mask airway, fentanyl, propofol, sevoflurane,nitrous oxide, and oxygen). Haemodynamic parameters were monitored and recorded. The requirements for

propofol, sevoflurane, and the postoperative need for ketobemidone were noted. The primary objectives of the study were were the number of PONV-free patients and patient satisfaction with respect to PONV. They concluded that coinduction with clonidine significantly increased the number of PONV-free patients after breast cancer surgery with general anesthesia.

Nishina, K : Mikawa, K : Maekawa, N : Shiga, M : Obara, H [23] Anesthesiology. 1998 Apr; 88(4): 922-7 “Effects of oral clonidine premedication on plasma glucose and lipid homeostasis associated with exogenous glucose infusion in children” In this study the effect of oral clonidine premedication were investigated in children undergoing minor surgery. The conclusion of the study was that oral clonidine as the premedication reduces hyperglycemic response, may be by inhibiting the surgical stress-induced release of catecholamines and cortisol. Infusion of 2% of glucose maintained plasma glucose concentrations within physiologic ranges in children receiving clonidine

Kahoru nishina MD, Katsuya Mikawa MD, Takanobu uesugi MD, Hidefumi obara MD [24] Cat.inist pediatric anesthesia ISSN 1155-5645 2006 VOL 16,834-839 Oral clonidine premedication reduces minimum alveolar concentration of sevoflurane for laryngeal mask airway insertion in children The study was conducted to determine

whether oral clonidine premedication can reduce MAC of sevoflurane for laryngeal mask airway insertion in children. They concluded that Oral clonidine premedication reduced the MAC (EC50) and EC95 values of sevoflurane for laryngeal mask airway insertion by 38% and 28%, respectively.

. H. Bergendahl , P-A. Lönnqvist et al, Clonidine in paediatric anaesthesia[25] Clonidine in paediatric anaesthesia: review of the literature and comparison with benzodiazepines for premedication The aim of this study is to review the use of clonidine in paediatric anaesthesia and to propose clonidine as a good alternative to midazolam.

Feld , Lawrence H ,Negus ,Jean B ,White,Paul F [26] Anesthesiology 1990 nov ,73(5). They compared the efficacy of oral midazolam premedication in children with different doses of 0.25mg, 0.75 and placebo. They concluded that concluded that oral midazolam 0.5 to 0.75 mg/kg is an effective premedication for children undergoing out patient surgery. Midazolam when administered orally should be mixed with a sweetener such as oral acetaminophen because it is bitter.

Co Mc millan, IA spahr- Schopfer N Sikick E Hartiey [27] Can journal of anesthesia 1992 jan 29, 39(6),545-550 "Premedication of children with oral midazolam" It was a randomized double blind placebo controlled study .The safety and efficacy of different doses of oral midazolam 0.5, 0.75, 1mg/kg given orally as premedication in children were compared. From this study, they concluded that Oral midazolam 0.5mg/kg is a

safe and effective premedication and 0.75 and 1mg/kg doses with no additional benefit may cause more side effects.

Parnis SJ ,foote JA,Vander walt JH,short T,crowe [28] NCBI , PUBMED GOV.Anesthesia intensive care 1992 feb ,20(1) ,9-14 27." Oral midazolam is an effective premedication for children having day stay anaesthesia" The effect of oral premedication was studied in a group of 200 children undergoing day stay anaesthesia. It was a double blinded, randomised trial . This study showed that a high proportion of unsedated children were calm at induction of anaesthesia They concluded that oral midazolam is an effective premedication in children for day-stay anaesthesia.

B craig Weldon MD, mehernoor F watha MD , paul F white Phd ,MD [29] Anesthesia analgesia 1992 , 75, 51-55" Oral midazolam in children :effect of time and adjunctive therapy" This study was conducted to determine the influence of timing and concomitant administration of atropine and/ or meperidine on the perioperative effects of oral midazolam in children. The conclusion of the study was that Midazolam (0.5 mg/kg) given orally 30-45 min before induction of anesthesia is safe and effective without delaying recovery after an ambulatory surgery.

Bredhl C ,Knudsen L, stjernholm PH ,mandoe H,Grevy C,KirkengardL ,Jensen S [30] Ncbi ,pubmed.gov 1994 june 27;156(26) 3897-9000] Midazolam and Lorazepam as premedication .In this randomized double blinded study oral midazolam and oral lorazepam were compared as premedication in a double-blind randomized clinical trial.The study was conducted in a group of 80 patients undergoing gynecological

procedures under general anaesthesia and a group of 80 patients undergoing hip arthroplasty under spinal anaesthesia .In the general anaesthesia group oral midazolam produced less postoperative sedation, less postoperative amnesia and their cognitive functions returned more rapidly. In the spinal anaesthesia group cognitive function returned more rapidly after midazolam .They concluded that Midazolam would be a better option if rapid recovery is desired.

Riva j, Lejbusiewicz G,papa M,Lauber C,Kohn W, dafonte M [31] Ncbi ; pubmed .gov paediatric anesthesia 1997;7(3) 191-6 . Oral premedication with midazolam in paediatric anaesthesia : effects on sedation and gastric contents. It was suggested that oral midazolam is an efficient and safe drug for premedication in paediatric anaesthesia.

Kain ZN, Mayes LC, Wang SM, Caramico LA, Hofstadter MB [32] Pubmed 1998 Nov;89(5):1147-56 ‘ Parental presence during induction of anesthesia versus sedative premedication: which intervention is more effective”. The midazolam and parental presence at the time of induction of anesthesia were used to treat preoperative anxiety in children during the study. The objective of the study was to determine which of these two interventions is better .A total of 88 children were randomly assigned to one of three groups: (1) 0.5 mg/kg oral midazolam; (2) parental presence during induction of anesthesia; or (3) control (no parental presence or premedication). They used multiple behavioral measures of anxiety, to assess the effect of the intervention on the children and their parents. Finally the conclusion was that group which

received midazolam has better anxiolysis than the one with parents at the time of induction

Okcu, Kemal Murat, Guner, Aydintug, Yavuz Sinan, Gunaydin, Sencimen, Metin [33]. Military Medicine, Apr 2004 "Evaluation of Oral or Rectal Midazolam as conscious sedation for paediatric patients in oral surgery " In this study 2 different routes of midazolam was compared in view of acceptance of the mode of treatment and local anesthesia, level of amnesia, and adverse effects. Oral midazolam was given at dose of 0.5 mg/kg and rectal midazolam at dose of 0.35 mg/kg There were significant differences between the acceptance of the oral and rectal administration of midazolam. They found that significantly higher number of children exhibited acceptance of the oral administration of midazolam

Lonnqvist, Per-Arne; Morton, Neil S [34] Dec 2006 Research gate scientific work current opinion anaethesiolgy 01/01/2007;19(6) 617-21. "Paediatric day case anaesthesia and pain control "Oral clonidine premedication, new, safer local anaesthetic agents, ultrasound guidance for blocks and prolongation of single-injection caudal blocks with clonidine or ketamine are some of the recent developments. Guidelines for safe sedation and analgesia for procedures are available. Behavioural and cognitive changes can be seen in children after anaesthesia and surgery and parents should be informed of this possibility.

SH cray ,JL Dixon ,C M B Heard ,Selsby [35] Pediatric anesthesia 2007, jan 30 ,6(4),265-270 The aim of the study was to assess the efficacy of oral midazolam premedication for pediatric day case surgery The conclusion was that Oral

midazolam is useful in providing a calm behavior in those children with high observer anxiety scores.

JiFeng Feng, Xiao-Xia Wang, Yan-Yan Lu, Deng-ge Pang, Wei Peng, Jian-lan Mo [36] Journal of International Medical Research 2017 vol 45 pages 912-933 "Effects of dexmeditomidine versus midazolam for premedication in paediatric anaesthesia with sevoflurane":They performed a meta-analysis to compare the effects of dexmeditomidine and midazolam in paediatric anaesthesia with sevoflurane .They found that both groups had a similar incidence of unsatisfactory mask acceptance, emergence agitation, and postoperative nausea and vomiting .Their conclusion was that compared with midazolam, dexmeditomidine is beneficial in paediatric anaesthesia with sevoflurane because of its lower incidence of unsatisfactory sedation, parental separation, and rescue analgesia

MATERIALS AND METHODS

- **SETTING**: The study was conducted in a single centre, in a Teritiary teaching Hospital.
- **Study Design**: Prospective randomized double blinded study of 100 patients.

A study group of 100 patients of age group 4 -12 yrs undergoing tonsillectomy under general anaesthesia were selected. They were divided into 2 groups of 50 patients each by lots taking method. All even numbers were assigned to Group A and all odd numbers were assigned to Group B.

Group A (oral clonidine) received 4 mcg/kg 90 minutes before induction.

Group B (oral midazolam) received 0.5 mg/kg 90 minutes before induction

INCLUSION CRITERIA:

Age: 4-12 years

Both sexes

ASA 1-2

Malampatti 1 & 2

Tonsillectomy under GA

EXCLUSION CRITERIA

ASA 3-4

Malampatti 3 & 4

Children with CNS disorder

Obesity (weight >95 percentile)

METHODOLOGY

An Ethical committee approval from Institution and written consent from the parents were obtained .

In group A (Clonidine) :

100 µg/tab of clonidine was crushed into powder, dissolved in sugar syrup and given to the patients in the dose of 4µg/kg, 90 minutes prior to induction.100µg/ tablet was dissolved in 5ml of sugar solution and the dose calculated as per weight of children was given through mouth after getting consent from the older children and from the mother of smaller children.

In Group II (Midazolam) :

Preservative free parenteral form of midazolam in the strength of 5 mg/ml was given orally in the dose of 0.5 mg/kg 90 minutes prior to induction .In our study none of the children vomited or spit out the drug during administration. The reaction to drug administration was evaluated.

Scores [9]

1. Crying

2. Not crying.

After 90 minutes in Group I and after 90 minutes in Group II sedation level was graded by evaluating the child's appearance with the help of four point sedation score described as below.

Sedation Score [15]

1- Alert

2- Awake

3 - Drowsy

4- Asleep

The anxiety or emotional state of children while separating from mother, was assessed by using four point anxiety score .

Anxiety Score [15]

1. Crying

2. Anxious

3. Calm, but not cooperative

4. Calm, cooperative or asleep

Then we also observed the level of anxiety on application of mask (acceptance of mask), graded by using the following scores.

Mask acceptance [40]

1. Combative crying

2. Moderate fear of mask

3. Cooperative with assurance

4.Calm, cooperative

5.Asleep

Reaction to venopuncture[15]

The reaction at the time of intravenous cannulation was graded by using sedation and anxiety score at that point of time

Post operative Status

Post operative status was assessed by using Modified objective pain scores

Modified objective pain score

Tears

Absent	0
Present, but child can be consoled	1
Present and child cannot be consoled	2

Movements

Absent	0
Moderate agitation (does not sit still)	1
Intense agitation (risk of trauma)	2

Behavior

Sleeping or calm	0
Grimacing, trembling voice, can be calmed down	1
Frightened, sticks to parents, cannot be calmed down	2

All the patients were monitored with pulse oximetry, NIBP, ECG. IV line was secured with appropriate size IV cannula. The reaction to IV cannulation was assessed by sedation and anxiety scoring at the same time . They were preoxygenated with 100% O2 for 3 minutes before induction .Mask acceptance was graded by above scoring system .Grade 3 ,4 and 5 are satisfactory. Injection glycopyrollate 10 mcg/kg was given IV for all patients .They were induced with Injection propofol 2mg/kg, fentanyl 2mcg/kg ,atracurium 0.5mg/kg. They were intubated with appropriate sized cuffed endotracheal tube .All of them were intra operatively maintained with O2 ,N2O,Atracurium 0.1 mg/kg and sevoflurane 1%.At the end of the surgery all the patients were reversed with Inj Neostigmine 40 mcg/kg and glycopyrollate 10mcg/kg. All of them were extubated after adequate reversal of neuro muscular blockade .They were monitored through out the surgery for any complications and were recorded if any.

Statistical Analysis

The information collected from all the selected cases were recorded in a Master Chart. The collected data were analysed with IBM.SPSS statistics software 23.0 Version. To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean & S.D were used for continuous variables. To find the significant difference between the bivariate samples in Independent groups the Unpaired sample t-test was used. To find the significance in categorical data Chi-Square test and Fisher's Exact was used. In all the above statistical tools the probability value 0 .05 is considered as significant level.

OBSERVATION AND RESULTS

The PH of the solutions used were measured by using Merck PH indicator paper and confirmed by PH meter.

Table 1: Comparision of PH of Drugs

Group	PH
Clonidine	6.5
Midazolam	3.5

The PH of both drugs were more than 2.5 and therefore chance of chemical pneumonitis in case of aspiration is not there.

Demographic profiles of the patients : Table 2

Criteria	Clonidine(GroupI)	Midazolam(Group II)	Test of significance (P Value)
Age	6.92	7	0.853
Sex(Male/Female)	39/11	38/12	0.812
Weight(Kg)	23.44	23.7	0.837

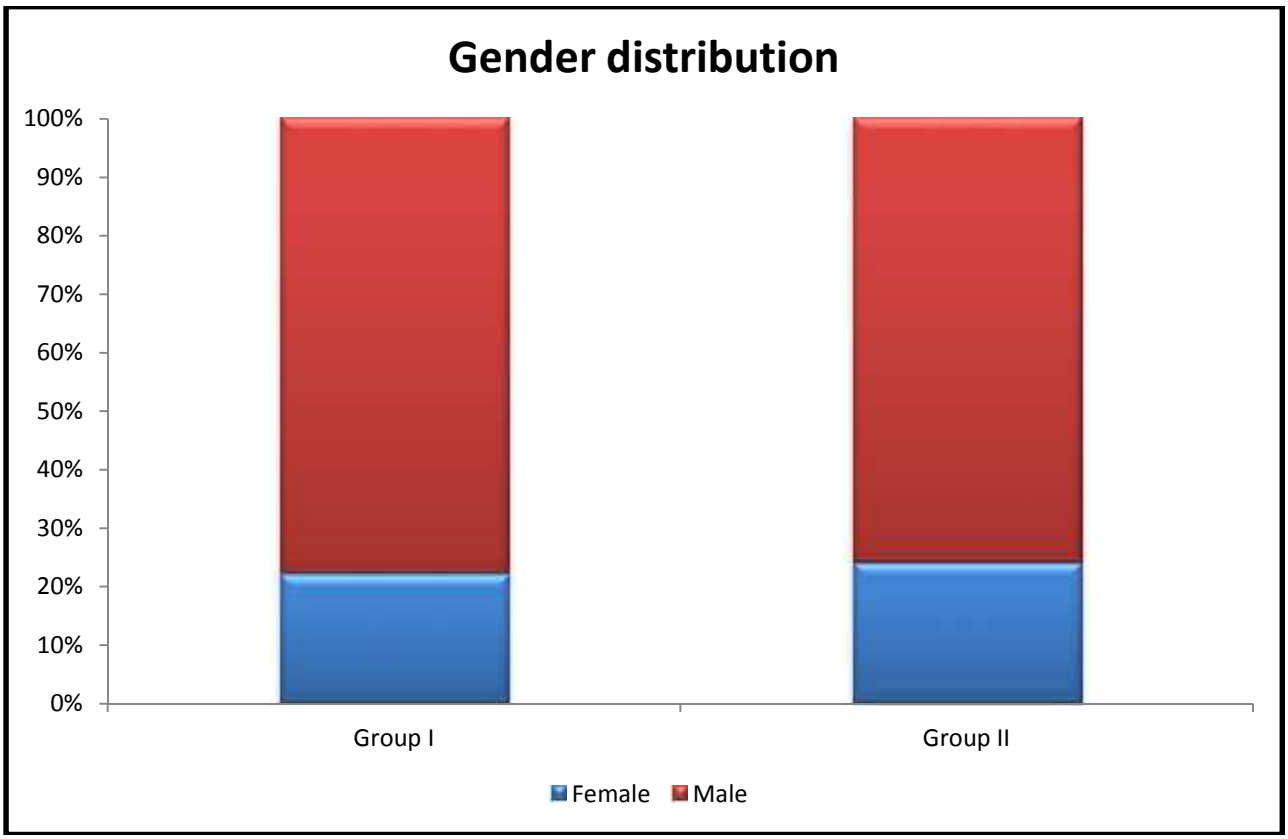
Significance of T Test for age 0.853, insignificant

Significance of Chi square Test for Sex 0.812, insignificant

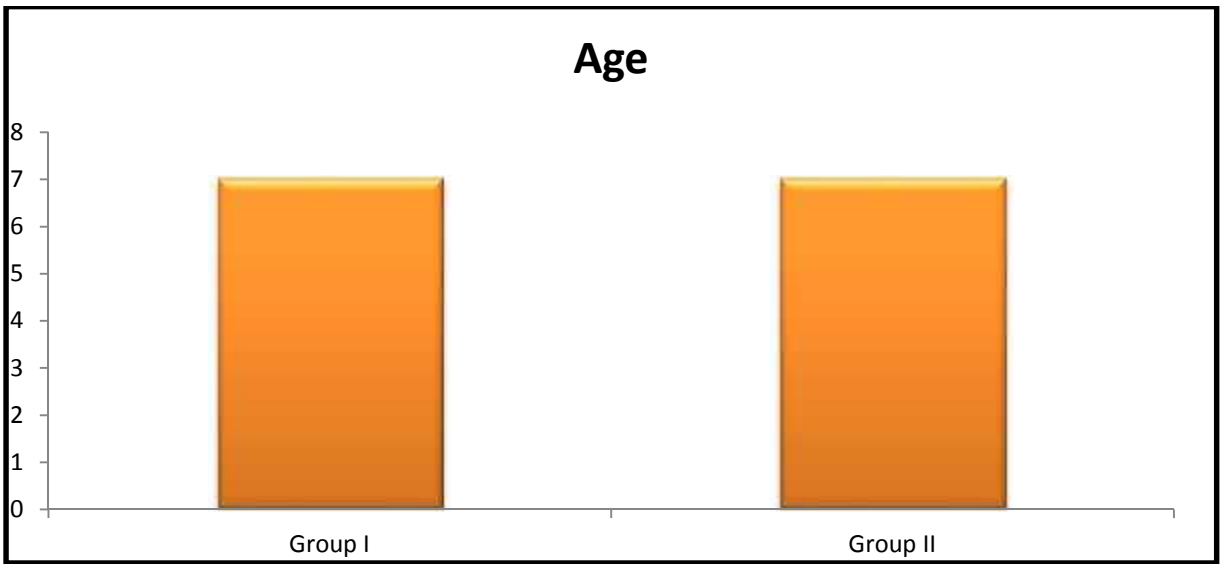
Significance of T Test for Weight 0.837, insignificant

Both our study groups were comparable with respect to age , sex and weight.

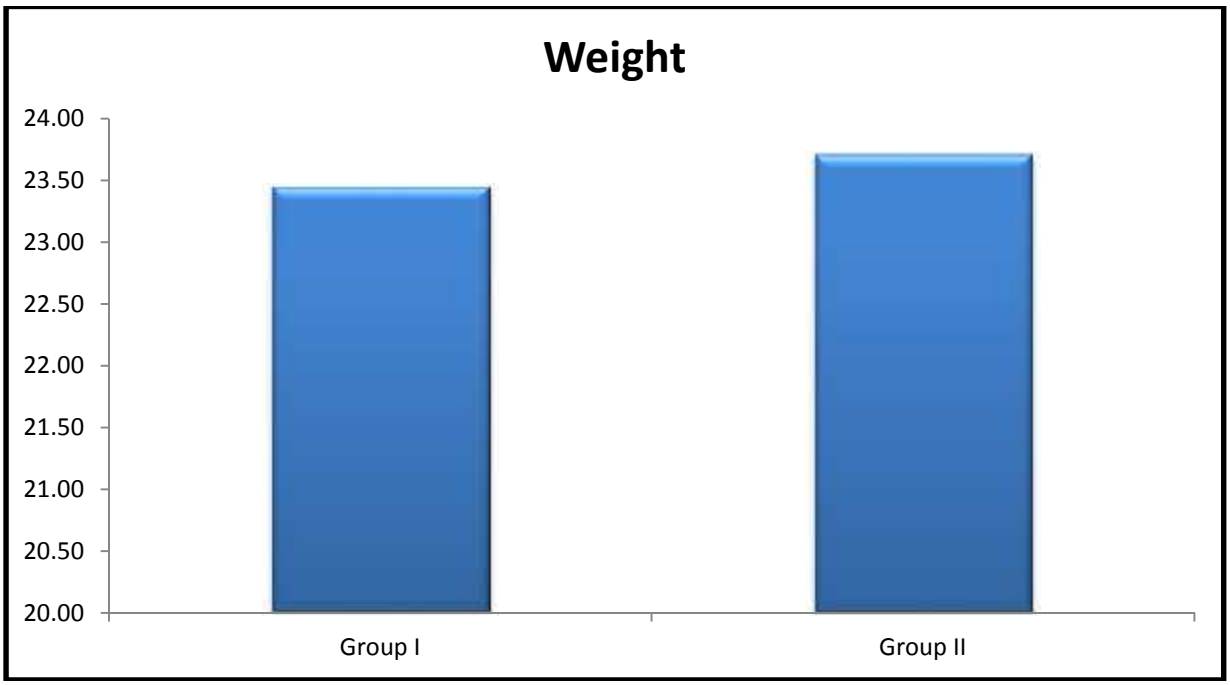
FIG[5]



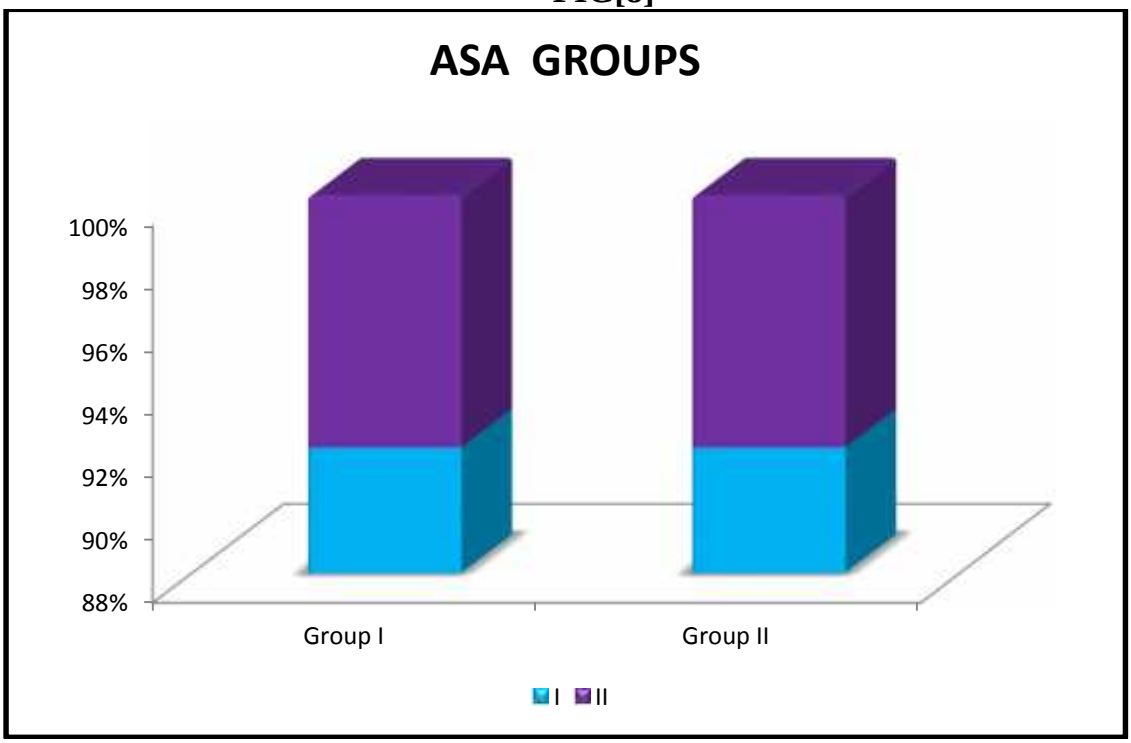
FIG[6]


Age
8
7
6
5
4
3
2
1
0
Group I
Group II

FIG[7]

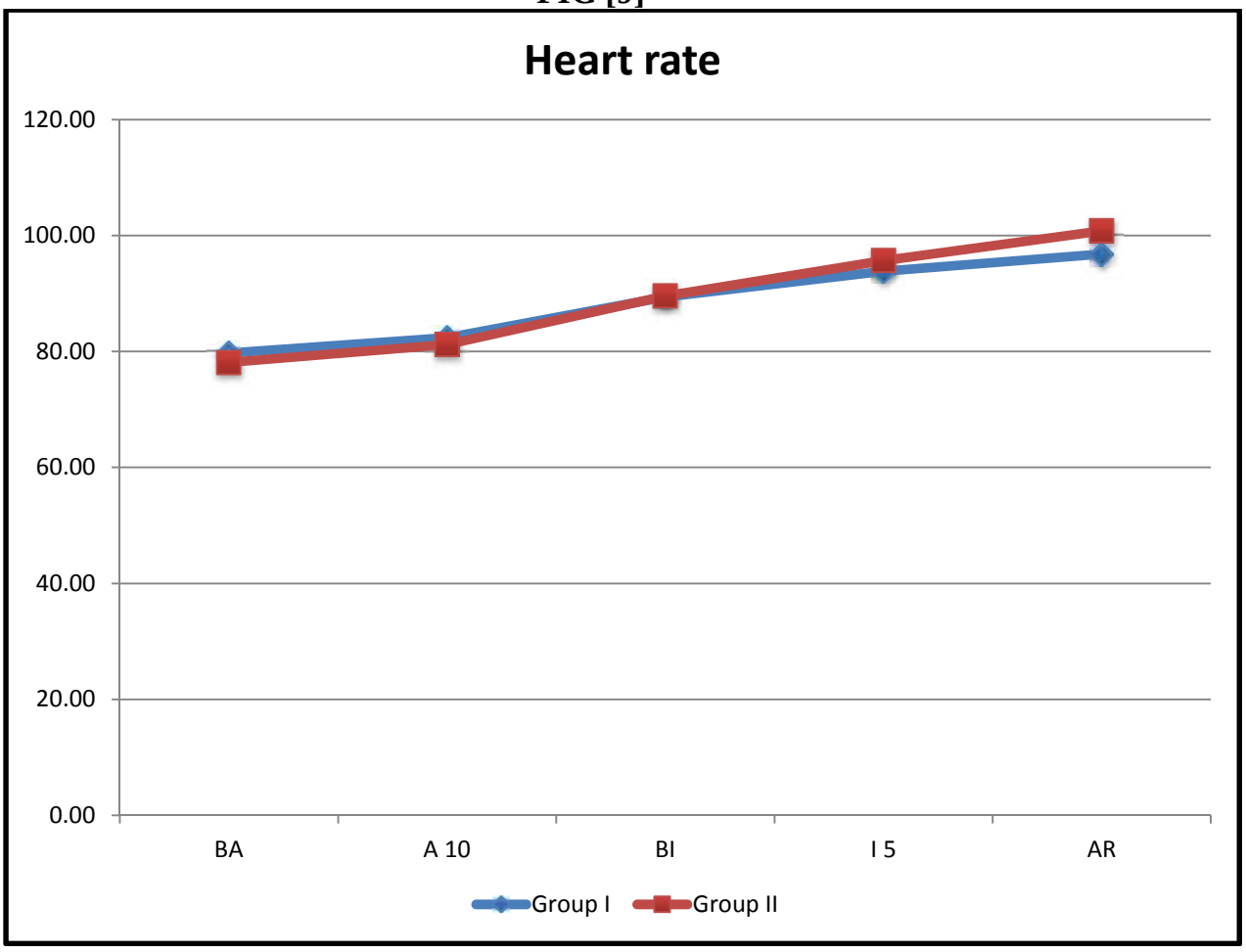

Weight
24.00
23.50
23.00
22.50
22.00
21.50
21.00
20.50
20.00
Group I
Group II

FIG[8]

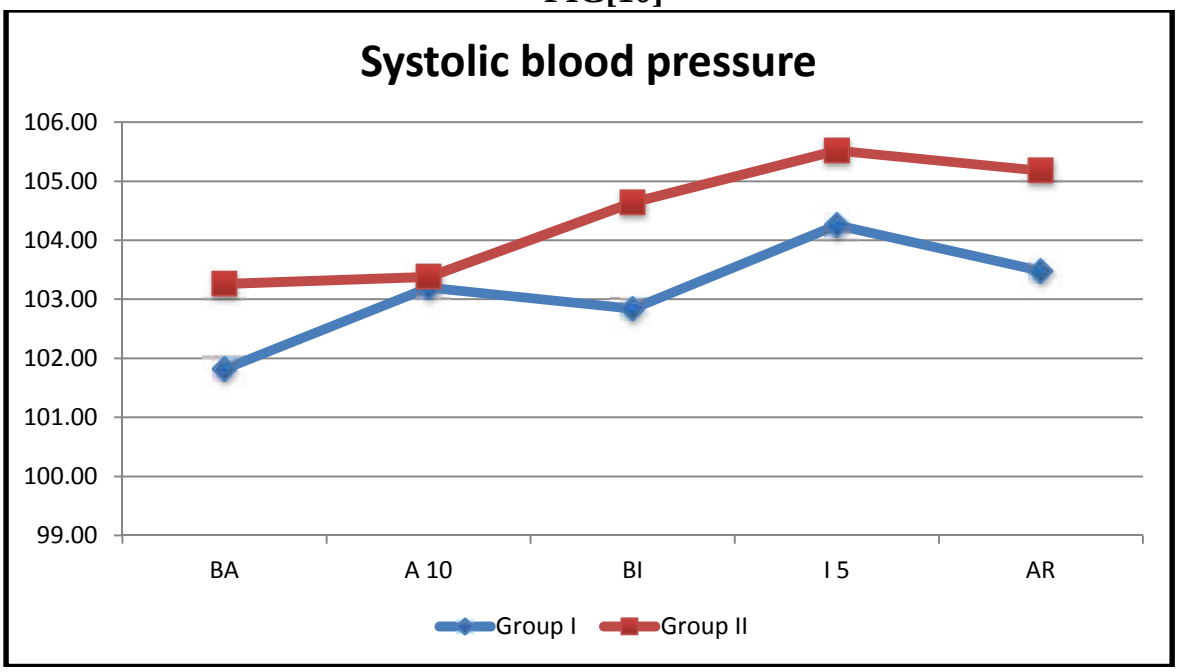


All the patients were heamodynamically stable through out the proceure and HR,BP and Spo2 were comparable between both the groups.

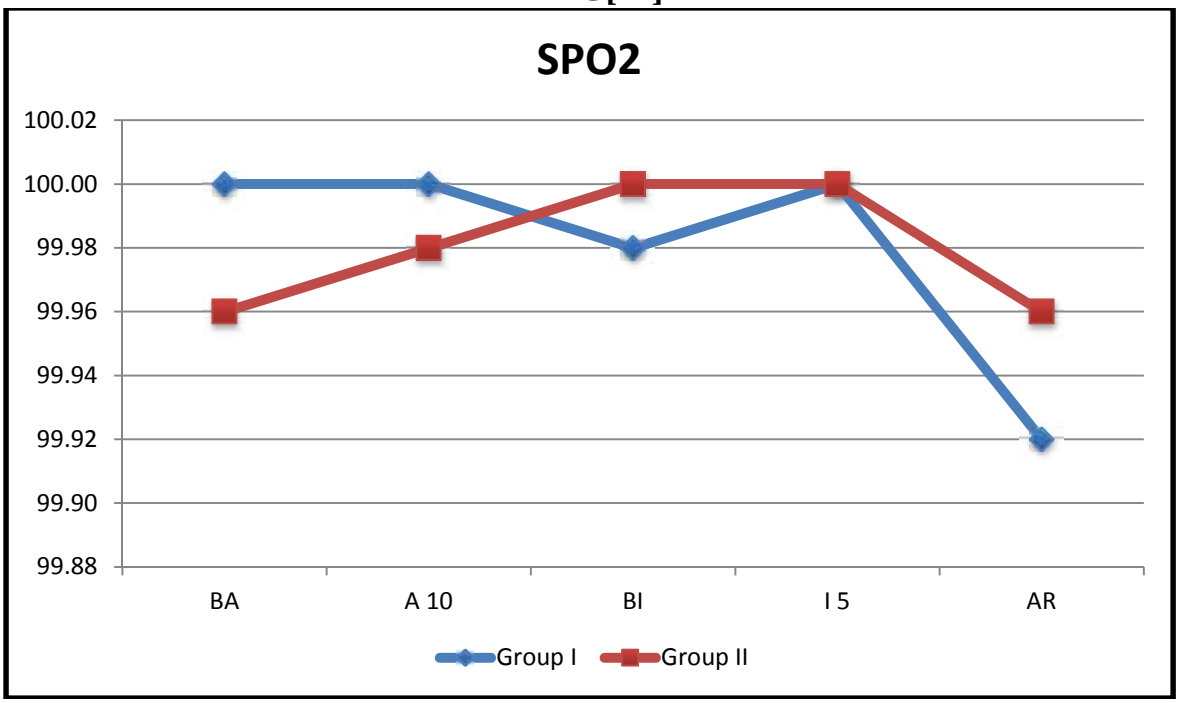
FIG [9]



FIG[10]


Systolic blood pressure
106.00
105.00
104.00
103.00
102.00
101.00
100.00
99.00
BA
A 10
BI
I 5
AR
Group I
Group II

FIG[11]

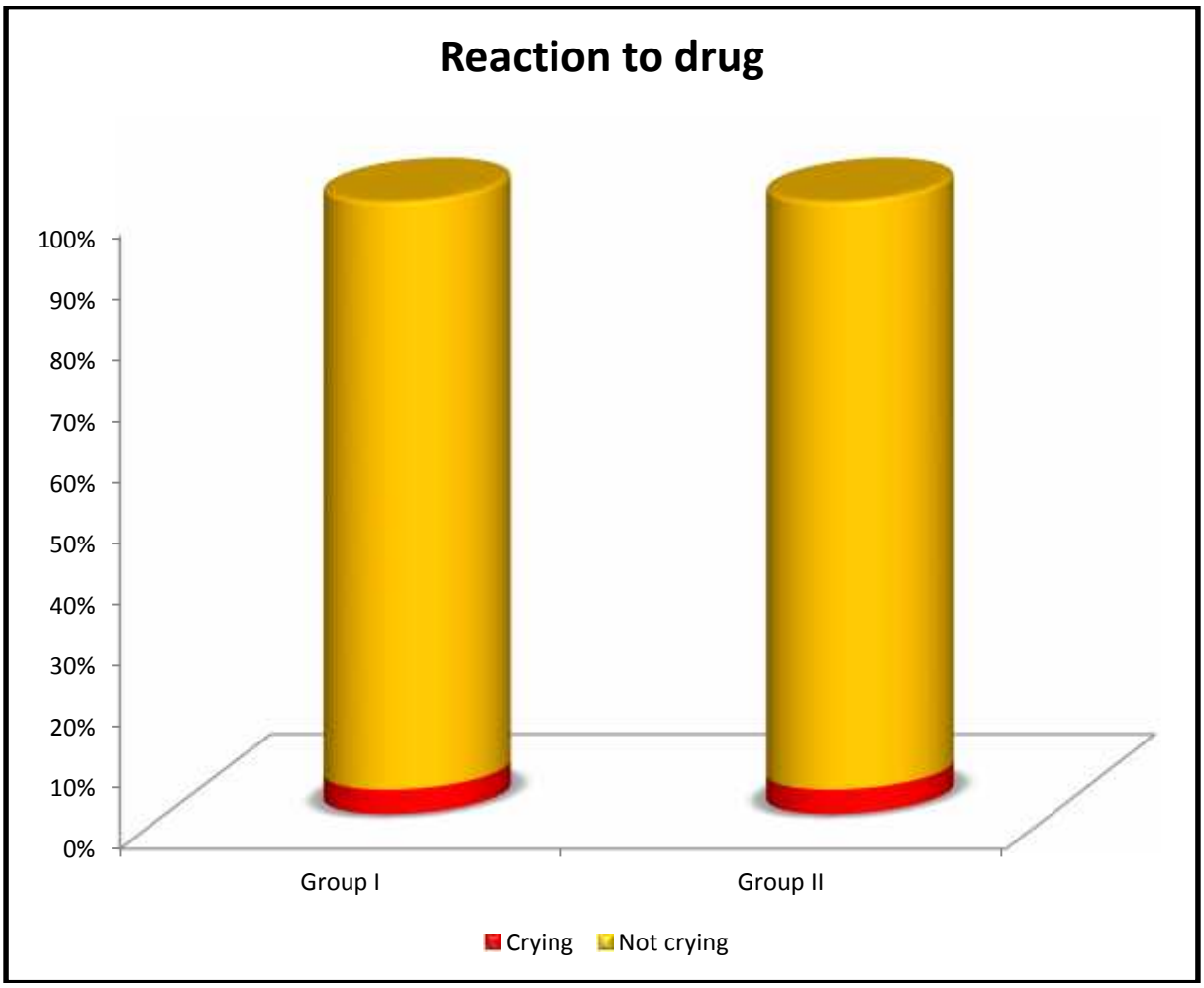

SPO2
100.02
100.00
99.98
99.96
99.94
99.92
99.90
99.88
BA
A 10
BI
I 5
AR
Group I
Group II

Reaction to Drug Administration: Table 3

Count		Group		Total
		clonidine	Midazolam	
Reaction to drug	Crying	3	2	4
	Not crying	47	48	95
Total		50	50	100

The number of children crying at the time of administration of drugs were comparable in both the study groups and was statistically insignificant

Fig[12]

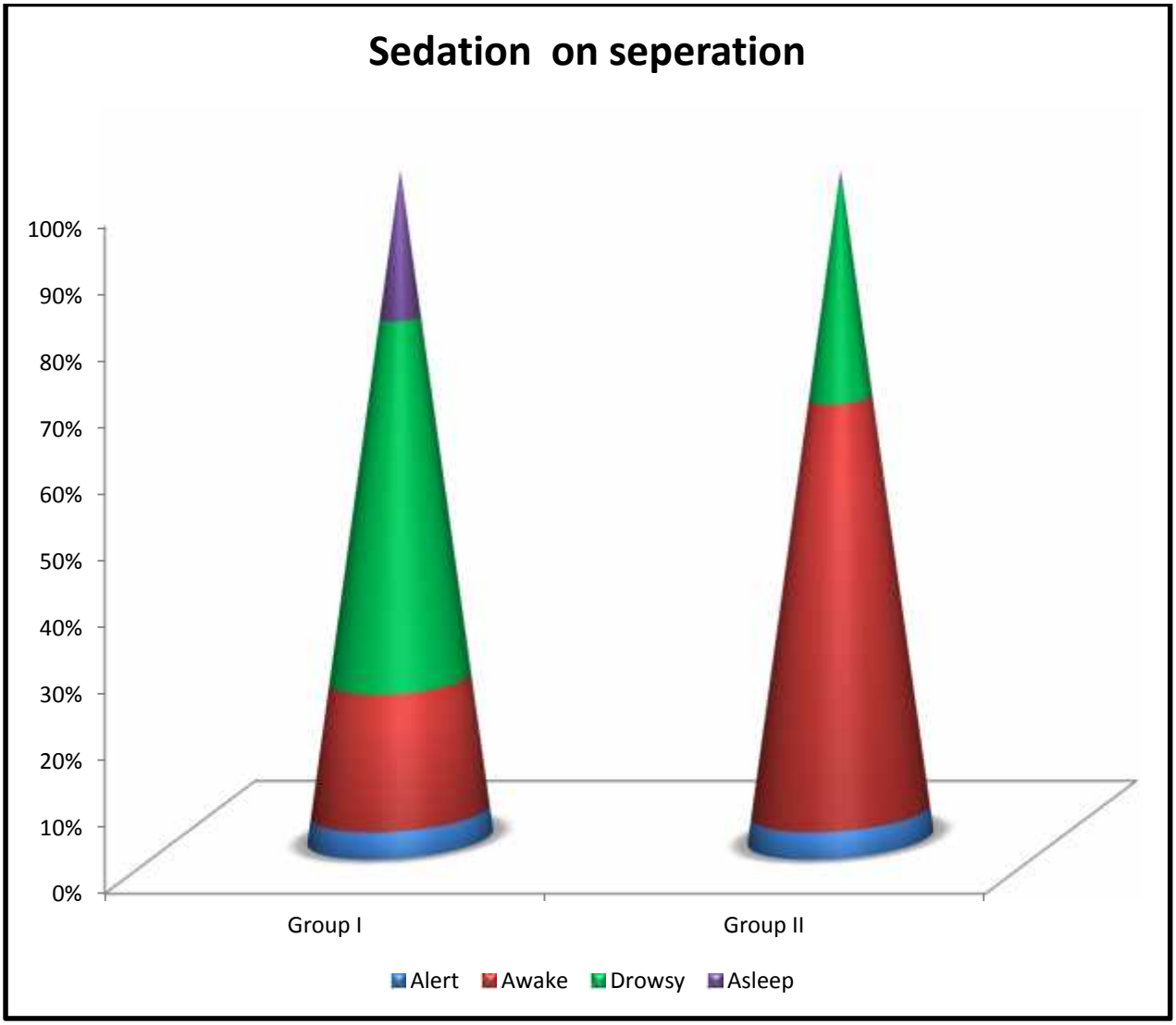

Reaction to drug
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Group I
Group II
Crying
Not crying

Intensity of sedation on separation from mother:Table 4

Score	Grade	Clonidine (Group I)	Midazolam (Group II)	Total
1	Alert	2	2	4
2	Awake	10	31	41
3	Drowsy	27	16	43
4	Sleep	11	1	12

11 children in clonidine group were asleep,27 were drowsy,10 were awake and 2 were alert at time of separation from parents.in midazolam group 1 was asleep,16 were drowsy,31 were awake and 2 were alert .the sedation score was found to be better in clonidine group with statistical significance of 0.000

FIG[13]

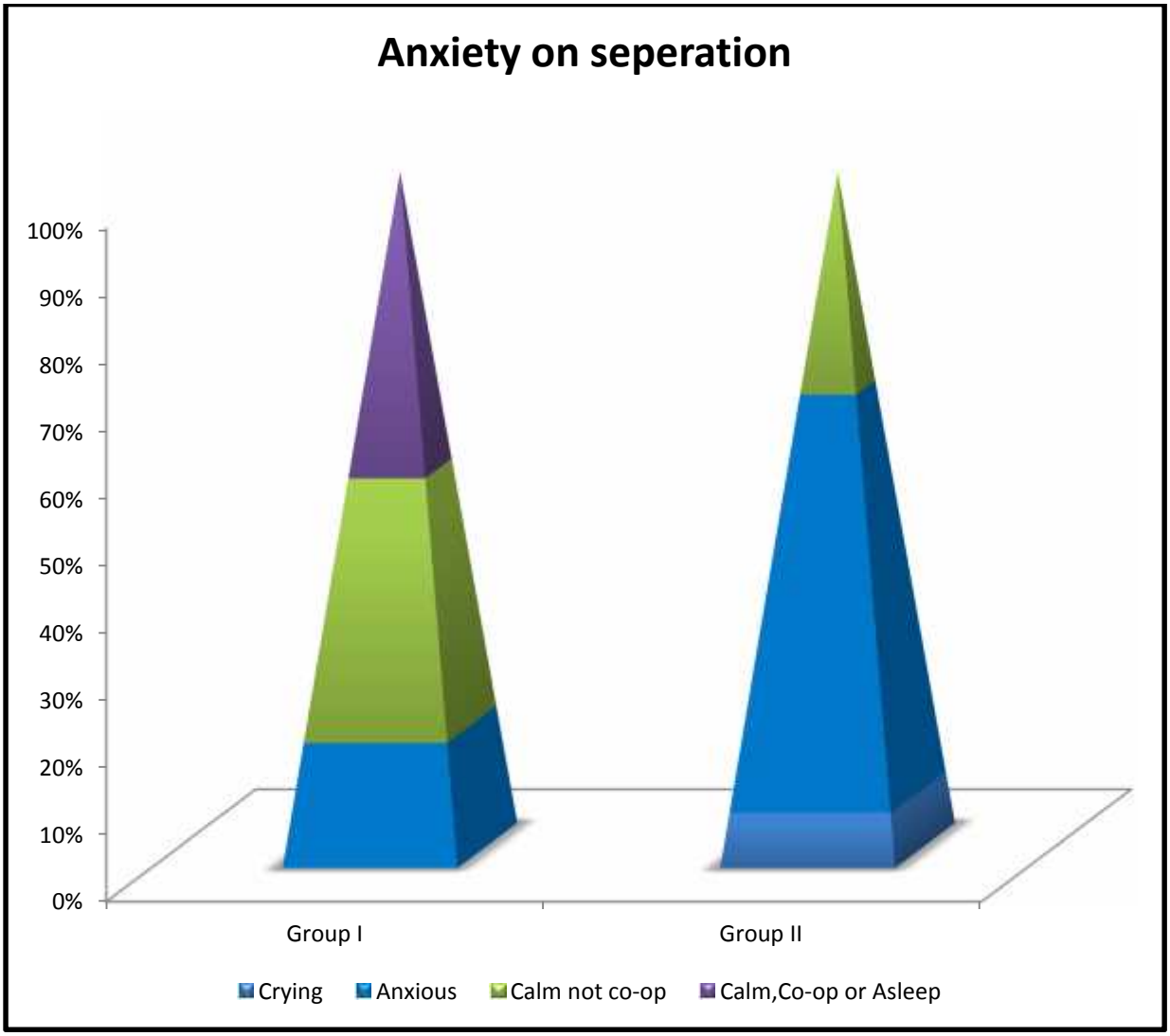

Sedation on seperation
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Group I
Group II
Alert
Awake
Drowsy
Asleep

Level of anxiety on separation from mother :Table 5

score	Grade	Clonidine (Group I)	Midazolam(Group	Total
1	Crying	0	4	4
2	Anxious	9	30	39
3	Calm/uncooperative	20	15	35
4	Calm/cooperative/Asleep	21	1	22

In clonidine group no children were crying,21 were calm and cooperative,19 were calm and uncooperative and 9 were anxious at the time of separation .In midazolam group 4 children were crying,30 were anxious,16 were calm and cooperative and 1 was calm and cooperative at the time of separation from the parents .The sedation score was better in clonidine group with a significance of 0.000

FIG[14]

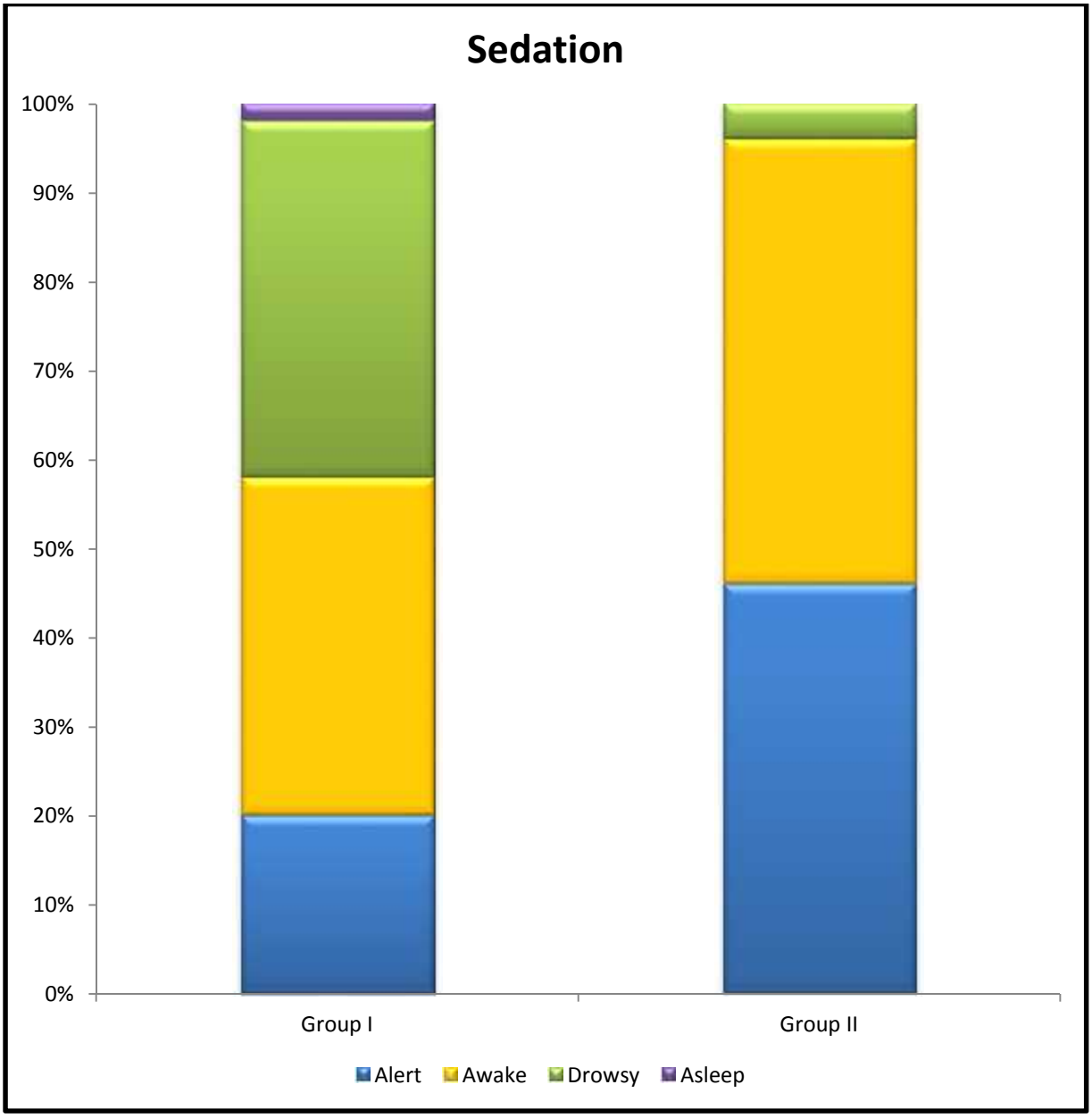

Anxiety on seperation
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Group I
Group II
Crying
Anxious
Calm not co-op
Calm,Co-op or Asleep

Intensity of sedation on Venopuncture :Table 6

Score	Grade	Clonidine(Group I)	Midazolam (Group II)	Total
1	Alert	10	23	33
2	Awake	19	25	44
3	Drowsy	20	2	22
4	Asleep	1	0	1

In the clonidine group 10 children were alert ,19 were awake at the time of venopuncture In the midazolam group 23 children were alert ,25 were awake at time of venopuncture. The sedation was found to be better in clonidine group than in midazolam with statistical significance of 0.000 which is highly significant.

FIG[15]

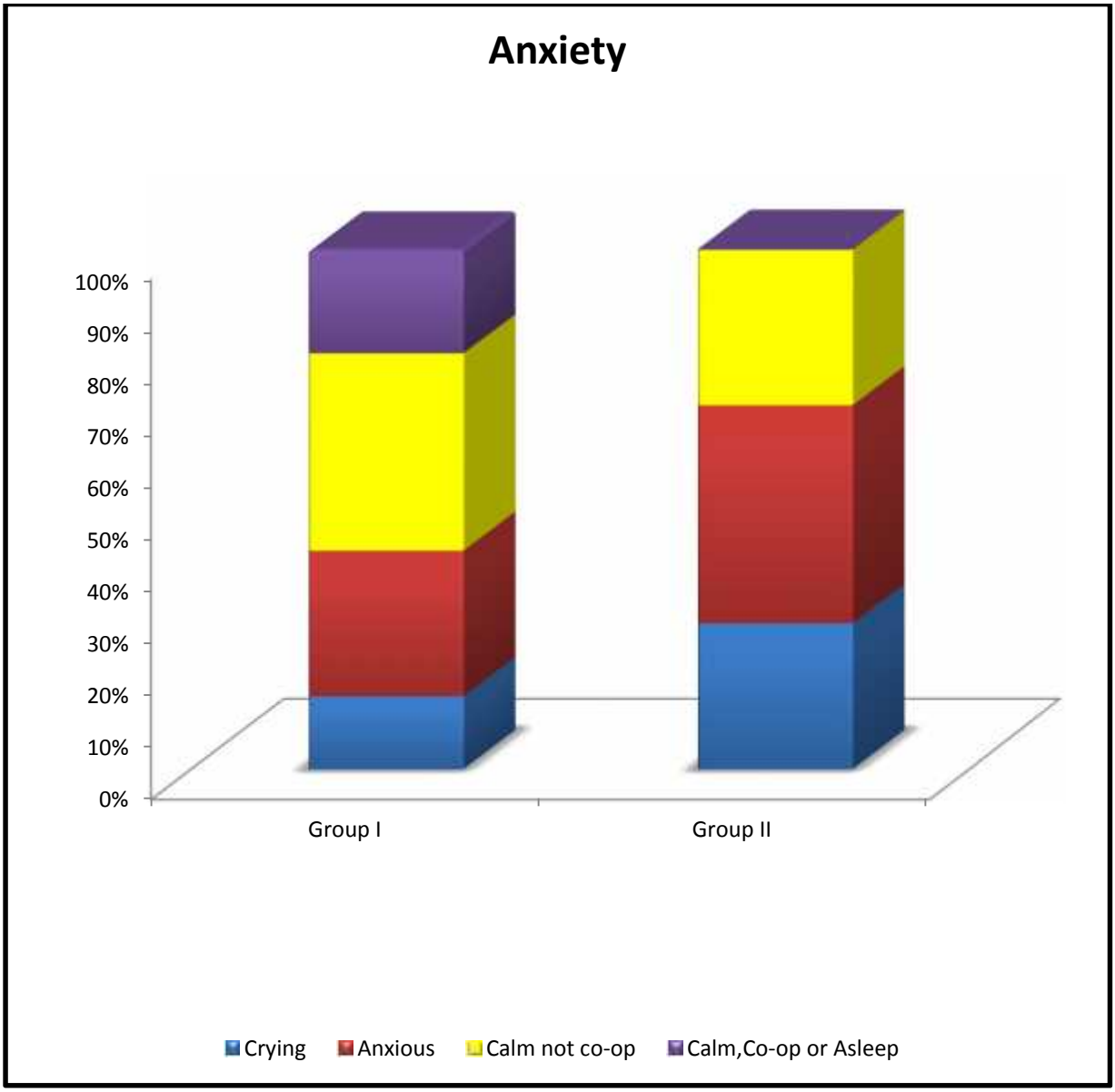

Sedation
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Group I
Group II
Alert
Awake
Drowsy
Asleep

Level of Anxiety on Venopuncture :Table 7

Score	Grade	Clonidine(Group I)	Midazolam (Group II)	Total
1	Crying	**7**	14	21
2	Anxious	14	21	35
3	Calm/Uncooperative	19	15	34
4	Calm/cooperative /asleep	10	0	10

In the clonidine group 7 children were crying,14 were anxious at the time of venopuncture in the midazolam group 14 were crying ,21 were anxious at the time of venopuncture. The anxiety score was better in clonidine group with statistical significance of 0.003

FIG[16]



GroupI :Clonidine

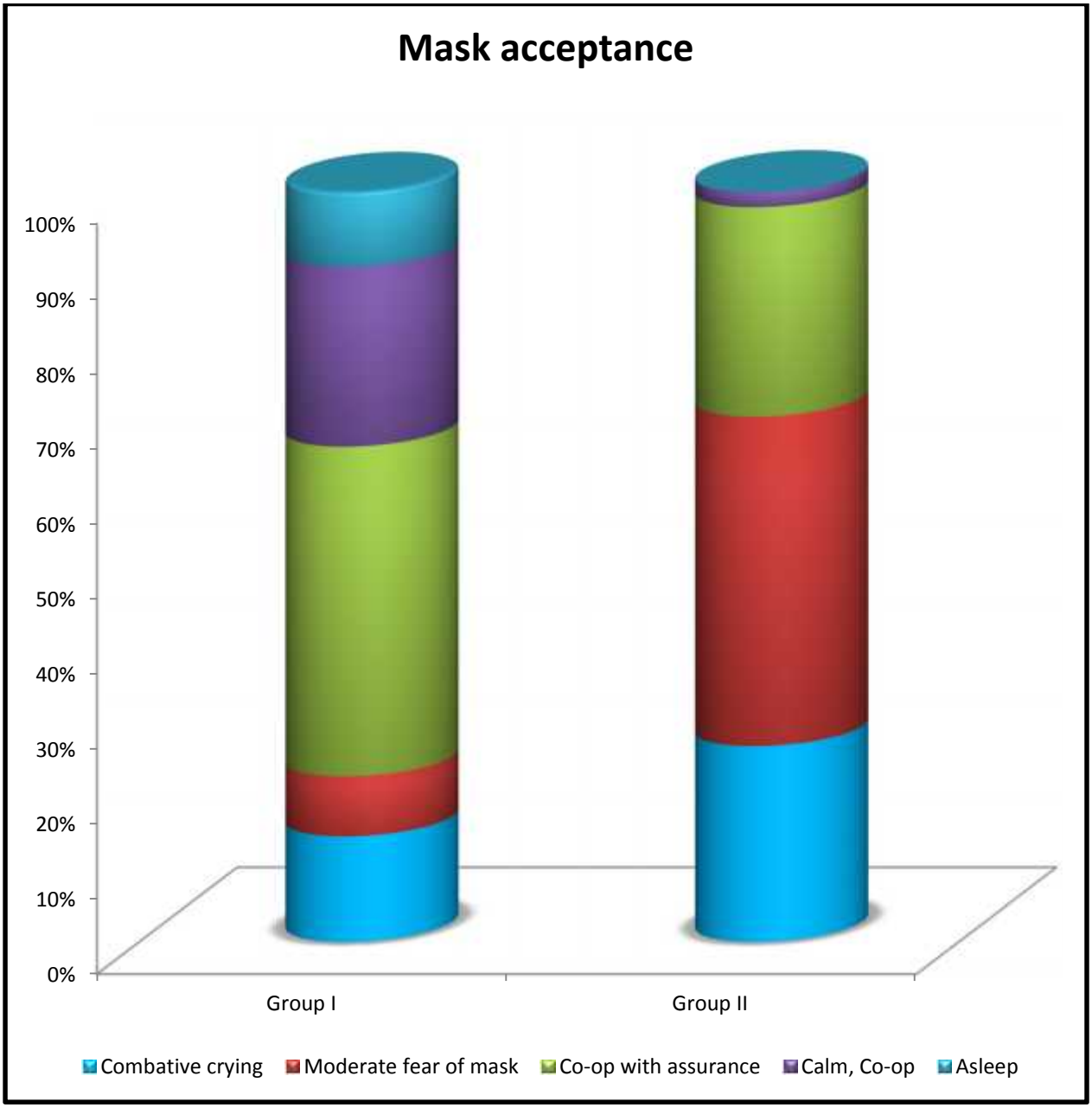
GroupII :Midazolam

Mask Acceptance : Table 8

Score	Grade	Clonidine (Group I)	Midazolam (GroupII)	Total
1	Combative/crying	7	13	20
2	Moderate fear for mask	4	22	26
3	Cooperative on assurance	22	14	36
4	Calm/cooperative	12	1	13
5	Asleep	5	0	5

In the clonidine group 12 children were calm and cooperative ,5 were asleep,22 were cooperative on assurance on face mask application .In the midazolam group 13 children were crying,14 were cooperative on assurance and one was calm and cooperative on mask application .Hence Mask acceptance was better in clonidine group with statistical significance of 0.000.

FIG[17]



Group I:Clonidine

Group II:Midazolam

Post Operative Status : Table 9

Groups	Score1	Score 2	Score3
Clonidine(Group I)	11	32	7
Midazolam(Group II)	0	31	19
Total	11	63	26

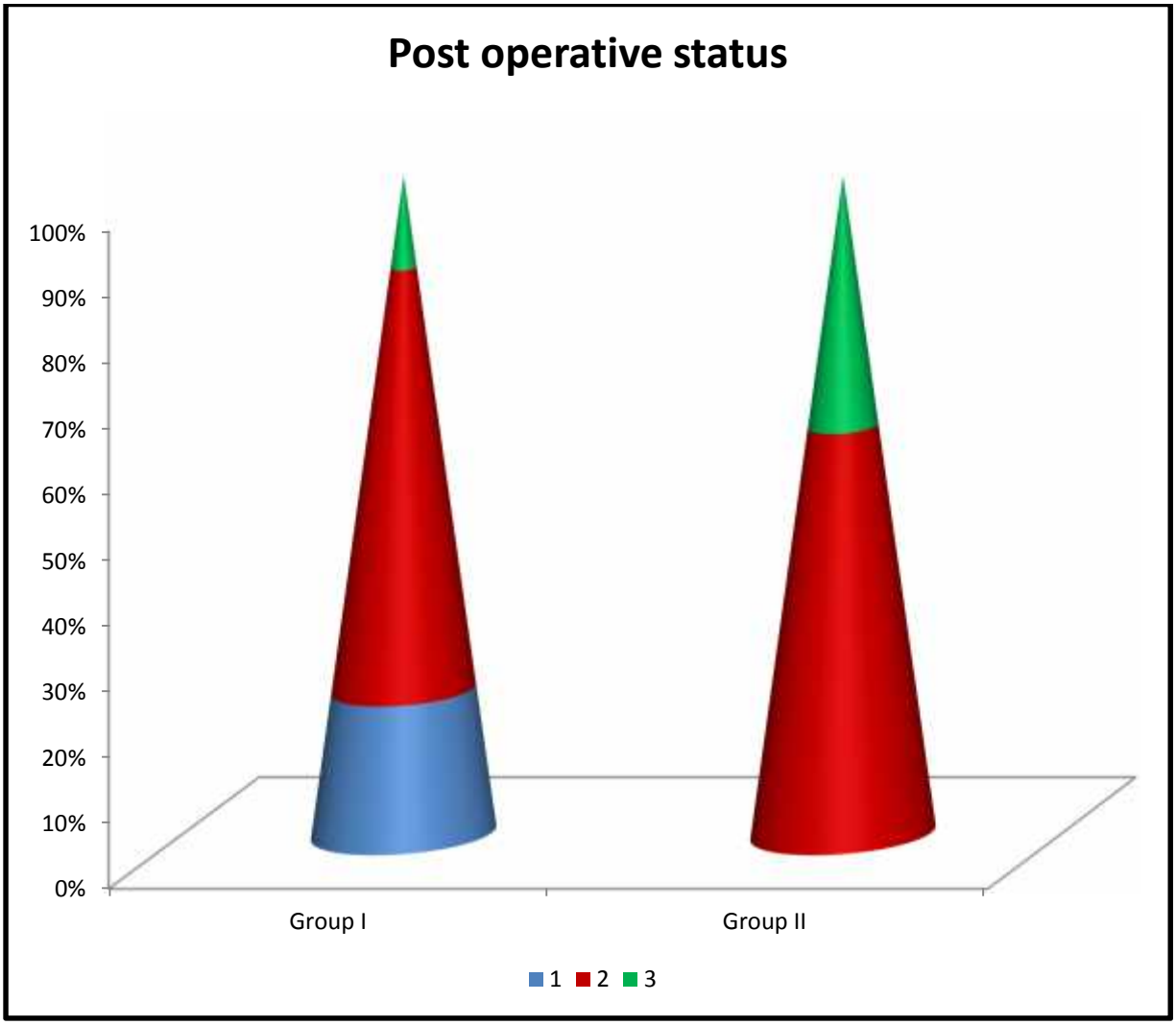
The post operative status was assessed 30 minutes after extubation in post operative care room.

In the clonidine group 11 children had tears and could be consoled with score of 1 ,32 children had tears and facial grimace with a score of 2 and 7 children had tears, moderate agitation and facial grimace with a score of 3.

In midazolam group 31 children had tears and facial grimace with score of 2 and 19 children had tears ,moderate agitation and facial grimace with a score of 3

The clonidine group had better post operative status than the midazolam group with a statistical significance of 0.000

FIG[18]



GroupI: Clonidine

GroupII: Midazolam

DISCUSSION

The practice of anesthetic premedication was introduced soon after ether and chloroform were introduced as general anesthetics in the middle of the 19th century[7]. By applying opioids ,benzodiazepines and anticholinergics before surgery, the patients undergoing surgery can achieve a less anxious state, and they would also acquire a smoother course during the tedious and dangerous induction stage. Premedication with opioids and anticholinergics was not a routine practice till the 20th century when intravenous anesthetics were primarily used as induction agents that significantly shorten the induction time. In the ancient preanaesthetic days even wine and opium were given to lessen the terror of surgery .The current practice of anesthetic premedication incorporates several aspects of patient care such as decreasing anxiety, dampening intraoperative noxious stimulus and its associated neuro endocrinological changes, and reducing postoperative adverse effects of anesthesia and surgery.

The concept of anesthetic premedication was developed in 1850s in order to counteract the side effects of general anesthesia when ether and chloroform were widely used as inhalational anesthetics [7].In 1864 Nussbaum in Germany and Bernard in France, found out simultaneously that subcutaneous morphine can relax patients and intensify chloroform anesthesia. Around the same time, another French scientist named Dastre found that atropine can decrease salivation and antagonize the effects of respiratory depression and vomiting associated with morphine. There after morphine and atropine became popular anesthetic premedication in the late 19th century. It was not popularized until Dudley Buxton published the first paper

regarding the use of morphine, atropine, scopolamine, and other similar agents prior to inhalation anesthesia in 1911.

Clonidine an alpha 2 agonist used as antihypertensive agent has been proved to have sedative and analgesic effect, prevents post operative nausea and vomiting. It has been under clinical trial as an efficient premedicant utilizing these properties of the drug.

Midazolam has been proved to be effective in reducing the preoperative anxiety level in many studies [26-36]. It was found that discharge from the recovery room in outpatient surgery was also not delayed in midazolam used patients. Except for midazolam, a2-agonists, antidepressants, and anticonvulsants are all effective in reducing the preoperative anxiety level

In our study we compared oral midazolam and oral clonidine as premedication in children undergoing tonsillectomy.

Anaesthesia and surgery creates a great psychological stress in most of the patients .The overall frequency of anxiety before anaesthesia was found to be 40 –60% in older children in a study conducted by Norris and Davis 1960) [6] as many as around 80% of patients were found to be anxious in an extensive study conducted by Corman et al in 1958 by using a psychological questionnaire[7] . A greater frequency was found in females than in males.

Premedication was considered essential in children. The pilot study showed that premedicated children had better value of arterial oxygen saturation than unpremedicated anxious and apprehensive children. A positive correlation was reported between anxiolysis and ease of induction of anaesthesia (Lindgren, Saarni Vaara, Himberg 1980)[37] .This supports the importance of the anxiolytic components of premedication. The relief of apprehension may reduce excessive hormonal and circulatory responses to anaesthesia and may reduce the minimum effective dose of anaesthetic agents [23,24]. Sedation was considered an useful property of premedicant drug [24,25,26].

In our study we used tablet form of clonidine dissolved in sugar syrup and given to the patient. . According to Teebeut et al [42] gastric contents with PH less than 2.5 is notorious to cause aspiration pneumonitis. The pH of the prepared clonidine solution is 6.5 and that of midazolam was 3.5 which is more than conservative pH limit of 2.5 thought to promote lung damage after aspiration of gastric contents.We noted a better profile with clonidine when compared to midazolam with respect to PH

The drug was very well accepted without spitting or vomiting by none patients in our study group. Mikawa et al compared two doses of oral clonidine (2µg and 4 µg) along with oral atropine 0.03mg/kg and concluded that 4 µg/kg is an effective dose for premedication [18].Therefore we used 4 µg/kg of clonidine in the study[18].According to British Pharmacopeia, midazolam is practically insoluble in

water, freely soluble in acetone, ethanol and methanol [37]. Mcmillan et al compared different doses of midazolam (0.5mg ,0.75mg and 1 mg/kg) and used the parenteral form of midazolam and concluded that 0.5mg/kg is safe and effective premedication[27]. In our study we used parenteral form of preservative free midazolam available in the in the strength of 5 mg/ml in the dose of 0.5 mg/kg.

Nicole Almenrader et al [9] conducted a prospective open study in 64 children .They were randomly alloted to receive either oral midazolam 0.5 mg / kg or oral clonidine 4µg/kg as premedication.This study helps to demonstrate clinical advantages of oral clonidine, in the preoperative period as well as recovery period compared to oral midazolam. Clonidine produced good sedation in 100% of patients of their study population .In clonidine premedication group 90% of children were asleep before mask induction were as in midazolam group only 10% were asleep .Clonidine causes sedation similar to natural sleep .in the clonidine group patient can be easily aroused to perform cognitive tests. This effect is thought to result from inhibition of spontaneous and evoked activity of central mono aminergic systems involved in modulation of sleep and cortical arousal .In our study, 76% of the patients in clonidine group has sedation scores of 3 and 4 while 34% of patients in midazolam group of the same scores while separation from the parents .

Kain et al[32] selected a group of children and were randomly assigned to one of three groups: (1) 0.5 mg/kg oral midazolam; (2) parental presence during induction of anesthesia; or (3) control (no parental presence or premedication). They used multiple behavioral measures of anxiety, to assess the effect of the intervention on the children and their parents. Finally they concluded that group which received midazolam has

better anxiolysis than the one with parents at the time of induction. In our study, regarding anxiety level on separation from parents, 80% of patients in the clonidine group are calm/cooperative but only 34% of patients in the midazolam group are calm / cooperative.

Trevour et al [15] found that 33.3% of children belonging to clonidine group were adequately sedated when compared to 23.3% of children in midazolam group at the time of veno puncture with statistical significance .They found that anxiolysis was better with midazolam group.In our study ,42% of patients in clonidine group had sedation scores of 3 and 4 and only 4% of patients in midazolam group had sedation score of 3 during venopuncture. Regarding the anxiety level at the time of venopuncture ,58% of patients in the clonidine group were calm/ cooperative but only 30% of patients in midazolam group were calm and cooperative .We founded that children belonging to clonidine group showed better outcome in sedation level and anxiolysis when compared to midazolam group, which was statistically highly significant.

Almenrader et al [9] study they found that mask acceptance was comparable between oral clonidine and oral midazalom.Mikawa et al[18] founded that mask acceptance was better in patients premedicated with 4mcg/kg clonidine in comparision with clonidine 2mcg/kg and diazepam[18].In our study, level of mask acceptance when compared 34% of patients in clonidine had score of 4 and 5 and only 2% of patients in the midazolam group had a score of 4 .So we noted that mask acceptance was better in clonidine group than midazolam group.

Almarander et al [9] found that more emergence agitation was associated with midazolam premedication .The clonidine group had better post operative recovery and significant parental satisfaction .In our study the post operative score graded as 3 according to Modified objective pain score was 14% in the clonidine group and was 38% in the midazolam group .Hence post operative score was also better in the clonidine group.post operative agitation was seen more in the midazolam group.

During the conduct of the study we didnt encounter any bradycardia ,hypotension and respiratory depression.All patient were premedicated with 10 mcg/kg glycopyrrolate

SUMMARY

In summary we found that both the test drugs produced significant sedation, clonidine produced better sedation than midazolam. Both the drugs provided statistically significant reduction of anxiety level on intravenous cannulation but it was better with the clonidine group.The mask acceptance was also better in clonidine group .Post operative agitation was lesser in clonidine group. Children accepted the technique well and parents were satisfied with the outcome. We were able to conduct the study in a busy government hospital with the co-operation of our nurses in the preoperative area.

CONCLUSION

We concluded from our study that oral clonidine and midazolam can be used as better premedicants to produce optimal sedation and emotional state .Clonidine 4 μg / kg has been shown to be a more effective premedication for children undergoing elective tonsillectomy than midazolam 0.5mg/kg.

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PROFORMA

Name: Age

Weight: Sex

ASA Risk:

Pre-medication Drug Dose:

Reaction to Drug

Score	**Reaction**
1	Crying
2	Not Crying

Seadation on separation

Score	**Sedation level**
1	Alert
2	Awake
3	Drowsy
4	Asleep

Anxiety on Seperation

Score	**Anxiety level**
1	Crying
2	Anxious
3	Calm, but not cooperative
4	Calm, cooperative or asleep

Sedation level on Venopuncture

Score	Sedation level
1	Alert
2	Awake
3	Drowsy
4	Asleep

Anxiety level on veno puncture

Score	Anxiety level
1	Crying
2	Anxious
3	Calm, but not cooperative
4	Calm, cooperative or asleep

Acceptance of face mask

Score	Level of acceptances
1	Combative crying
2	Moderate fear of mask
3	Cooperative with assurance
4	Calm, cooperative
5	Asleep

Modified objective pain score

Tears

Absent	0
Present, but child can be consoled	1
Present and child cannot be consoled	2

Movements

Absent	0
Moderate agitation (does not sit still)	1
Intense agitation (risk of trauma)	2

Behavior

Sleeping or calm	0
Grimacing, trembling voice, can be calmed down	1
Frightened, sticks to parents, cannot be calmed down	2

ORAL CLONIDINE

SL	Age	Sex	ASA	Weight	Reaction to drug	Sedation on seperation	Anxiety on seperation	Reaction to IV cannula		Mask acceptance	postoperative status	Heart Rate					Systolic BP					SPO2				
								Sedation	Anxiety			BA	A10	BI	I5	AR	BA	A10	BI	I5	AR	BA	A10	BI	I5	AR
1	5	Male	I	17	2	3	3	2	3	4	2	75	72	85	80	95	100	110	100	110	100	100	100	100	100	100
2	7	Male	I	20	2	4	4	3	3	4	1	80	85	88	90	99	102	98	106	104	102	100	100	100	100	100
3	4	Female	I	14	2	3	4	3	3	4	1	74	85	88	99	100	112	105	100	106	102	100	100	100	100	100
4	5	Male	I	22	2	3	3	2	2	3	2	75	86	88	90	100	115	114	100	110	108	100	100	100	100	100
5	9	Male	I	25	2	4	4	3	4	4	1	86	90	92	99	100	104	100	104	114	106	100	100	100	100	100
6	6	Male	I	22	2	3	4	2	3	3	2	72	80	95	99	95	98	100	102	110	100	100	100	100	100	99
7	8	Male	I	25	2	2	3	1	2	2	2	75	78	86	92	95	102	110	106	115	105	100	100	100	100	100
8	5	Female	II	20	2	4	4	3	3	4	2	72	76	88	94	85	100	105	108	104	110	100	100	100	100	100
9	6	Male	I	25	2	3	3	2	3	3	2	75	78	76	90	99	107	104	110	106	100	100	100	100	100	100
10	10	Male	I	32	2	3	4	3	4	4	2	88	88	99	91	90	102	112	98	100	102	100	100	100	100	100
11	4	Female	I	15	2	4	4	3	4	4	1	75	78	99	85	95	92	94	99	100	98	100	100	100	100	100
12	5	Male	I	18	2	3	3	3	3	3	2	76	78	89	99	95	100	98	102	106	94	100	100	100	100	100
13	7	Male	I	28	2	3	3	2	3	2	3	80	84	90	99	100	102	100	105	110	100	100	100	100	100	99
14	7	Female	I	23	2	2	2	1	2	2	3	85	88	94	94	100	100	105	110	102	100	100	100	100	100	100
15	8	Male	II	28	2	3	4	2	2	3	2	89	82	99	100	95	106	110	105	104	112	100	100	100	100	100
16	6	Male	I	22	2	3	3	3	3	3	2	88	84	90	95	94	96	95	98	100	102	100	100	100	100	100
17	5	Male	I	19	2	4	4	3	4	4	1	84	85	94	94	99	95	98	96	99	100	100	100	99	100	100
18	6	Female	I	22	2	3	3	2	2	3	2	74	80	95	97	111	95	96	94	98	98	100	100	100	100	100
19	11	Male	I	32	2	4	4	3	3	4	2	86	88	95	94	100	102	110	105	107	106	100	100	100	100	99
20	4	Male	I	12	1	4	4	3	3	4	2	84	86	94	99	100	98	94	96	94	98	100	100	100	100	100
21	5	Male	I	18	2	3	3	2	3	3	2	85	84	94	99	95	100	94	99	100	102	100	100	100	100	100
22	7	Female	I	24	2	2	2	2	1	1	2	81	85	92	100	101	102	110	105	106	110	100	100	100	100	100
23	4	Male	I	14	2	3	3	2	2	2	2	83	85	94	98	95	98	100	96	102	110	100	100	100	100	100
24	7	Male	I	22	2	3	3	2	2	3	1	85	81	90	95	98	102	110	104	101	100	100	100	100	100	100
25	5	Male	II	19	2	4	4	4	4	4	2	84	85	90	94	99	100	98	105	104	100	100	100	100	100	100
26	11	Male	I	30	2	1	2	1	1	1	3	85	82	95	92	89	112	110	105	114	106	100	100	100	100	100
27	11	Female	I	28	2	2	2	1	2	3	2	78	85	90	95	99	114	112	110	105	102	100	100	100	100	100
28	4	Male	I	14	2	3	3	3	2	3	2	84	85	84	90	99	94	98	95	100	102	100	100	100	100	100
29	6	Male	I	21	2	2	2	1	1	1	2	88	94	99	100	95	98	98	96	94	100	100	100	100	100	100
30	4	Female	I	14	1	3	4	3	4	4	1	81	85	90	94	90	94	98	92	100	102	100	100	100	100	99
31	8	Male	I	33	2	1	2	1	1	1	2	85	84	94	98	98	100	105	106	100	102	100	100	100	100	100
32	7	Female	I	32	2	3	4	2	3	3	2	84	88	89	94	99	104	100	102	110	105	100	100	100	100	100
33	6	Male	I	22	2	3	3	2	3	3	1	84	86	88	95	99	100	102	108	110	106	100	100	100	100	100
34	8	Male	I	25	2	3	3	3	3	3	2	84	82	88	94	95	102	105	112	105	106	100	100	100	100	100
35	9	Female	I	27	2	3	4	3	3	3	2	77	81	90	94	99	110	106	102	104	112	100	100	100	100	100
36	7	Male	I	28	2	3	4	2	3	4	1	80	85	88	90	94	98	100	102	104	105	100	100	100	100	100
37	6	Male	I	25	2	2	3	1	2	3	2	71	75	82	95	99	100	102	104	99	98	100	100	100	100	100
38	8	Male	I	26	2	3	4	2	3	4	2	70	78	85	88	94	100	102	110	102	106	100	100	100	100	100
39	5	Male	I	20	2	4	4	3	4	3	1	76	78	80	95	98	95	98	94	100	105	100	100	100	100	100
40	11	Male	I	31	2	3	4	2	3	4	1	75	72	86	88	95	105	110	104	106	102	100	100	100	100	100
41	6	Male	I	20	2	2	3	1	2	3	2	72	76	80	88	94	100	102	105	104	110	100	100	100	100	100
42	7	Male	I	24	2	3	3	3	2	3	3	77	80	85	94	99	102	104	103	102	100	100	100	100	100	100
43	10	Male	I	31	2	2	2	1	1	1	3	75	78	80	88	99	112	110	105	112	108	100	100	100	100	100
44	8	Male	I	29	2	3	3	2	2	3	2	80	86	97	99	100	105	112	102	105	108	100	100	100	100	100

ORAL CLONIDINE

SL	Age	Sex	ASA	Weight	Reaction to drug	Sedation on seperation	Anxiety on seperation	Reaction to IV cannula		Mask acceptance	postoperative status	Heart Rate					Systolic BP					SPO2				
								Sedation	Anxiety			BA	A10	BI	I5	AR	BA	A10	BI	I5	AR	BA	A10	BI	I5	AR
45	5	Male	I	17	2	4	4	3	4	4	2	85	86	90	95	92	100	102	106	104	106	100	100	100	100	100
46	4	Female	I	12	2	4	4	3	4	3	2	74	78	84	88	94	100	102	98	94	98	100	100	100	100	100
47	12	Male	I	36	2	3	3	2	2	3	3	85	84	88	95	92	98	105	110	106	102	100	100	100	100	100
48	10	Male	I	31	2	3	4	3	4	4	2	72	75	80	88	95	102	103	102	110	106	100	100	100	100	100
49	8	Male	II	26	2	2	2	1	1	1	2	81	86	90	99	100	110	102	106	105	102	100	100	100	100	100
50	9	Male	I	32	2	2	2	2	1	1	3	75	82	86	92	99	106	102	110	106	110	100	100	100	100	100

ORAL MIDAZOLAM

SL	Age	Sex	ASA	Weight	Reaction to Drug	Sedation at sepeartion	Anxiety at sepeartion	Reaction to IV cannula		Mask Acceptance	Post Operative status	Heart Rate					Systolic BP					SPO2				
								Sedation	Anxiety			BA	A10	BI	I5	AR	BA	A10	BI	I5	AR	BA	A10	BI	I5	AR
1	7	Male	I	30	2	2	2	2	1	1	2	75	78	85	99	92	98	105	100	108	100	100	100	100	100	100
2	4	Male	I	16	2	2	3	2	2	2	2	72	78	85	90	99	106	100	106	110	102	100	100	100	100	100
3	8	Female	I	28	2	3	3	2	3	3	2	80	85	88	96	91	110	105	102	105	102	100	100	100	100	100
4	6	Male	I	25	2	2	2	1	1	1	2	86	88	84	97	100	115	118	100	120	108	100	100	100	100	100
5	6	Female	I	24	2	2	2	2	3	2	3	85	88	82	99	100	104	98	109	110	106	100	100	100	100	100
6	4	Male	I	13	2	3	2	2	2	3	2	75	78	84	99	110	98	100	102	110	100	100	100	100	100	100
7	9	Male	I	28	2	2	2	2	1	1	2	88	90	92	90	99	102	106	110	112	104	100	100	100	100	100
8	11	Female	I	32	2	3	3	3	2	3	2	76	80	90	92	95	100	105	104	110	110	100	100	100	100	100
9	5	Female	I	16	2	3	3	2	1	1	2	80	82	88	92	96	101	106	114	108	108	100	100	100	100	100
10	5	Male	I	18	2	2	2	1	2	2	3	81	85	85	95	99	102	112	98	100	102	100	100	100	100	100
11	7	Male	I	26	2	3	3	2	2	3	2	80	89	82	96	106	96	99	100	102	98	100	100	100	100	100
12	9	Female	I	25	2	3	2	2	3	2	3	82	81	85	90	96	102	95	100	105	99	98	100	100	100	100
13	5	Male	II	16	2	2	2	1	2	2	3	80	85	90	91	98	102	100	106	105	100	100	100	100	100	100
14	12	Male	I	37	2	2	2	1	1	1	2	85	86	84	96	105	112	102	115	106	110	100	100	100	100	100
15	6	Male	I	22	2	2	2	1	1	1	3	75	78	90	99	107	104	106	102	110	112	100	100	100	100	100
16	8	Male	I	29	2	2	2	1	2	2	2	76	75	82	94	99	95	99	94	100	105	100	100	100	100	100
17	6	Female	I	19	2	2	2	1	2	2	2	81	85	90	90	95	98	100	102	100	105	100	100	100	100	100
18	8	Male	I	27	2	3	2	2	3	2	3	78	80	84	95	100	98	100	94	98	100	100	100	100	100	100
19	9	Male	I	31	2	2	1	1	1	1	3	79	75	80	99	111	104	110	102	104	108	100	100	100	100	100
20	7	Male	I	24	2	2	2	1	2	2	2	86	84	90	95	94	99	85	96	99	100	100	99	100	100	99
21	5	Male	I	18	2	2	3	2	3	2	2	82	85	96	98	102	102	98	100	102	104	100	100	100	100	100
22	5	Male	II	17	2	2	2	2	2	2	3	78	76	82	99	100	116	110	102	110	112	100	100	100	100	100
23	9	Male	I	28	2	3	2	2	3	2	2	72	75	95	92	105	100	98	98	105	108	100	100	100	100	100
24	4	Male	I	14	1	2	2	2	3	2	3	70	72	92	95	106	104	112	106	101	110	100	100	100	100	100
25	7	Female	I	24	2	3	2	2	2	2	2	85	84	96	99	105	102	98	108	104	99	100	100	100	100	100
26	8	Male	I	30	2	2	2	1	1	1	3	82	84	94	98	108	114	106	118	109	106	100	100	100	100	100
27	5	Male	I	16	2	2	2	1	2	2	3	84	86	95	99	102	112	102	114	102	110	100	100	100	100	100
28	8	Male	I	30	2	3	1	2	1	1	3	82	88	99	100	110	98	95	96	100	104	100	100	100	100	100
29	9	Male	I	31	2	2	2	1	2	2	3	75	74	90	98	95	100	102	100	102	104	100	100	100	100	100
30	8	Female	I	26	2	2	2	1	2	2	2	74	78	90	95	99	98	100	94	100	105	100	100	100	100	100
31	7	Male	I	22	2	2	2	2	2	3	2	80	81	94	99	102	110	105	108	110	106	100	100	100	100	100
32	7	Female	I	23	2	2	3	1	2	3	2	74	72	95	98	105	105	100	110	112	108	100	100	100	100	100
33	4	Female	I	12	1	1	1	1	1	1	2	76	78	98	100	112	102	106	109	110	115	100	100	100	100	100
34	9	Male	I	28	2	3	3	2	3	3	2	80	85	89	96	98	102	105	112	105	106	100	100	100	100	100
35	11	Male	I	35	2	3	3	2	3	4	2	75	78	80	95	95	112	110	106	105	110	100	100	100	100	100
36	5	Male	I	17	2	3	2	2	2	3	2	72	78	86	92	102	100	102	106	104	102	100	100	100	100	100
37	7	Male	I	25	2	2	2	1	2	3	3	75	78	88	96	98	102	105	110	100	98	100	100	100	100	100
38	8	Male	II	28	2	2	2	1	1	1	2	80	88	98	95	99	102	106	112	106	104	100	100	100	100	100
39	6	Male	I	22	2	2	3	2	3	3	2	82	84	99	92	98	94	95	98	100	106	100	100	100	100	100
40	4	Male	I	13	2	2	3	2	2	3	3	78	76	88	92	99	105	108	105	108	102	100	100	100	100	100

ORAL MIDAZOLAM

SL	Age	Sex	ASA	Weight	Reaction to Drug	Sedation at sepeartion	Anxiety at sepeartion	Reaction to IV cannula		Mask Acceptance	Post Operative status	Heart Rate					Systolic BP					SPO2				
								Sedation	Anxiety			BA	A10	BI	I5	AR	BA	A10	BI	I5	AR	BA	A10	BI	I5	AR
41	8	Male	I	27	2	1	1	1	1	1	3	80	88	95	99	100	98	102	106	110	108	100	100	100	100	100
42	7	Male	I	28	2	2	3	2	3	3	3	74	78	85	95	99	106	110	106	104	98	100	100	100	100	100
43	5	Male	I	15	2	2	2	1	2	2	2	85	90	92	96	98	106	105	100	110	104	100	100	100	100	99
44	4	Male	I	14	2	2	3	1	1	1	3	75	78	80	90	99	110	114	112	108	106	100	100	100	100	100
45	6	Female	I	22	2	2	2	1	2	2	2	74	78	98	100	115	100	102	106	104	106	100	100	100	100	100
46	9	Male	I	31	2	3	3	2	3	2	2	75	78	95	96	100	98	102	100	94	102	100	100	100	100	100
47	12	Male	I	35	2	3	2	1	3	2	3	70	78	95	99	102	98	110	114	103	105	100	100	100	100	100
48	7	Female	I	22	2	4	3	3	3	3	2	70	75	90	95	98	102	103	102	110	106	100	100	100	100	100
49	8	Male	II	25	2	3	3	2	3	3	2	80	84	92	95	99	115	105	106	110	106	100	100	100	100	100
50	6	Male	I	21	2	2	2	1	1	2	2	68	85	95	99	100	104	102	112	106	120	100	100	100	100	100